Nevada Medicaid Drug Use Review Board Meeting

April 22, 2021

Table of Contents

Agenda	3
DUR Summary	8
DUR Board Meeting Minutes for January 28, 2020	11
Multiple Sclerosis Agents	30
Hereditary Angioedema Agents	81
Platelet Inhibitors	103
Narcolepsy Agents	133
Hepatitis C Treatments	220
Calcitonin Gene-Related Peptide (CGRP) Antagonists	263
Anticonvulsants	296
Board Requested Reports	330
Standard Reports	334

NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

Date of Posting:	March 3, 2021
Date of Meeting:	Thursday, April 22, 2021 at 1:00 PM
Name of Organization:	The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Drug Use Review Board (DUR).
Remote Meeting Access:	Microsoft Teams Or http://bit.ly/2Pt2tGI Out of deference to Declaration of Emergency Directive 006 from the State of Nevada Executive Department signed by Governor Sisolak on March 22, 2020 & Emergency Directive 003 signed March 20, 2020, a physical location will not be open to the public for attendance at this time. Note: *If at any time during the meeting an individual who has been named on the agenda or has an item specifically regarding them included on the agenda is unable to participate because of technical or other difficulties, please email Tanya Benitez at tbenitez@dhcfp.nv.gov and note at what time the difficulty started so that matters pertaining specifically to their participation may be continued to a future agenda if needed or otherwise addressed.*
Meeting Audio Information:	Follow the instructions that appear on your screen to join the audio portion of the meeting. Audio will be transmitted over the internet. **For Audio Only:** Phone: (952) 222-7450 Event: 882 990 774#

PLEASE DO NOT PUT THIS NUMBER ON HOLD (*hang up and rejoin if you must take another call*)

AGENDA

1. Call to Order and Roll Call

2. General Public Comment

(*Owing to the lack of a physical location for this meeting, public comment is encouraged to be submitted in advance so that it may be included in meeting materials and given attention. No action may be taken upon a matter raised through public comment unless the matter itself has been specifically included on an agenda as an action item. Please provide your name in any comment for record keeping purposes. You may submit comments in writing via e-mail to tbenitez@dhcfp.nv.gov. There may be opportunity to take public comment via telephone, but phone participants should disconnect their call and re-join if they must take another call. Do not place your phone on hold or you may disrupt the meeting for other participants. Public comment may be limited to three minutes per person.* **Note: this guidance regarding public comment applies throughout this agenda where public comment is referenced.**)

Public comments may be related to topics on the agenda or matters related to other topics per NRS 241.020(3)(3)(II).)

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from January 28, 2021.
b. Status Update by DHCFP.

4. Clinical Presentations

a. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Multiple Sclerosis (MS) Agents.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

b. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Hereditary Angioedema Agents.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

c. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Platelet Inhibitors.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

d. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for Narcolepsy Agents.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

e. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for Anti-Hepatitis Agents.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

f. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for Calcitonin Gene-Related Peptide (CGRP) Receptor Inhibitor Medications.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

g. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for Anticonvulsants.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

5. DUR Board Requested Reports

a. **For Possible Action**: Opioid utilization – top prescribers and members.

i. Discussion by the Board and review of utilization data.
ii. Requests for further evaluation or proposed clinical criteria to be presented at a later date.

6. Standard DUR Reports

a. Review of Prescribing/Program Trends.

i. Top 10 Therapeutic Classes for Q3 2020 and Q4 2020 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR).

i. Review of Q4 2020.
ii. Review of Top Encounters by Problem Type.

c. Retrospective Drug Utilization Review (RetroDUR).

i. Status of previous quarter.
ii. Status of current quarter.
iii. Review and discussion of responses.

7. Closing Discussion

a. Public comment.

(No action may be taken upon a matter raised under public comment period unless the matter itself has been specifically included on an agenda as an action item. Comments will be limited to three minutes per person. Persons making comment will be asked to begin by stating their name for the record and to spell their last name and provide the secretary with written comments.)

b. **For Possible Action**: Date and location of the next meeting.

c. Adjournment.

PLEASE NOTE: Items may be taken out of order at the discretion of the chairperson. Items may be combined for consideration by the public body. Items may be pulled or removed from the agenda at any time. If an action item is not completed within the time frame that has been allotted, that action item will be continued at a future time designated and announced at this meeting by the chairperson. All public comment may be limited to three minutes.

This notice and agenda have been posted online at http://dhcfp.nv.gov and http://notice.nv.gov, as well as Carson City, Las Vegas, and Reno central offices for the DHCFP. E-mail notice has been made to such individuals as have requested notice of meetings (to request notifications please contact tbenitez@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730). At this time, in deference to Emergency Directive 006 dated March 22, 2020 and related directives which have discouraged certain in-person activities, notice has not been posted at other physical locations.

If you require a physical copy of supporting material for the public meeting, please contact tbenitez@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730. Supporting material will also be posted online as referenced above.

Note: We are pleased to make reasonable accommodations for members of the public with a disability and wish to participate. If accommodated arrangements are necessary, notify the DHCFP as soon as possible and at least ten days in advance of the meeting, by e-mail at tbenitez@dhcfp.nv.gov in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 3: The requirements contained in NRS 241.020 (4)(a) that public notice agendas be posted at physical locations within the State of Nevada are suspended.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 4: Public bodies must still comply with requirements in NRS 241.020 (4)(b) and NRS 241.020 (4)(c) that public notice agendas be posted to Nevada's notice website and the public body's website, if it maintains one along with providing a copy to any person who has requested one via U.S. mail or electronic mail.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 5: The requirement contained in NRS 241.020 (3)(c) that physical locations be available for the public to receive supporting material for public meetings is suspended.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 6: If a public body holds a meeting and does not provide a physical location where supporting material is available to the public, the public body must provide on its public notice agenda the name and contact information for the person designated by the public body from whom a member of the public may request supporting material electronically and must post supporting material to the public body's website, if it maintains one.

Summary of the DUR Board

Drug Use Review Board

The Drug Use Review Board (DUR) is a requirement of the Social Security Act, Section 1927 and operates in accordance with Nevada Medicaid Services Manual, Chapter 1200 – Prescribed Drugs and Nevada Medicaid Operations Manual Chapter 200.

The DUR Board consists of no less than five members and no more than ten members appointed by the State Director of Health and Human Resources. Members must be licensed to practice in the State of Nevada and either an actively practicing physician or an actively practicing pharmacist.

The DUR Board meets quarterly to monitor drugs for:

- therapeutic appropriateness,
- over or under-utilization,
- therapeutic duplications,
- drug-disease contraindications
- quality care

The DUR Board does this by establishing prior authorization and quantity limits to certain drugs/drug classes based on utilization data, experience, and testimony presented at the DUR Board meetings. This includes retrospective evaluation of interventions, and prospective drug review that is done electronically for each prescription filled at the Point of Sale (POS).

Meetings are held quarterly and are open to the public. Anyone wishing to address the DUR Board may do so. Public comment is limited to five minutes per speaker/organization (due to time constraints). Anyone presenting documents for consideration must provide sufficient copies for each board member and a copy (electronic preferred) for the official record.

The mission of the Nevada DUR Board is to work with the agency to improve medication utilization in patients covered by Medicaid. The primary goal of drug utilization review is to enhance and improve the quality of pharmaceutical care and patient outcomes by encouraging optimal drug use.

Current Board Members:

Jennifer Wheeler, Pharm.D., Chair

Netochi Adeolokun, Pharm.D., Vice Chair

Mark Canty, MD

Crystal Castaneda, MD

Jessica Cate, Pharm.D.

Dave England, Pharm.D.

Mohammad Khan, MD

Brian Le, DO

Michael Owens, MD

Jim Tran, Pharm.D.

Drug Use Review (DUR) Board Meeting Schedule for 2021

Date	Time	Location
April 22, 2021	1:00 PM	Microsoft Teams
July 22, 2021	1:00 PM	TBD
October 14, 2021	1:00 PM	TBD

Web References

Medicaid Services Manual (MSM) Chapter 1200:

http://dhcfp.nv.gov/Resources/AdminSupport/Manuals/MSM/C1200/Chapter1200/

Drug Use Review Board Bylaws:

http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Boards/CPT/DUR_Bylaws_draft.pdf

Drug Use Review Board Meeting Material:

https://www.medicaid.nv.gov/providers/rx/dur/DURBoard.aspx

Social Security Act, 1927:

https://www.ssa.gov/OP_Home/ssact/title19/1927.htm

Meeting Minutes

Drug Use Review Board

Draft Meeting Minutes

Date of Meeting:	Thursday, January 28, 2021
Name of Organization:	The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Drug Use Review Board

Agenda Item	Record	Notes
1. Call to Order and Roll Call	Chairwoman Wheeler called the meeting to order at 1:17 p.m. on January 28, 2021. The roll was taken by Chairwoman Wheeler. Jennifer Wheeler, Pharm.D., Chair ☒ Present ☐ Absent Netochi Adeolokun, Pharm.D., Vice Chair ☒ Present ☐ Absent Mark Canty, MD ☐ Present ☒ Absent Crystal Castaneda, MD ☒ Present ☐ Absent Jessica Cate, Pharm.D. ☐ Present ☒ Absent Dave England, Pharm.D. ☒ Present ☐ Absent Mohammad Khan, MD ☒ Present ☐ Absent Brian Le, DO ☒ Present ☐ Absent Michael Owens, MD ☐ Present ☒ Absent Jim Tran, Pharm.D. ☐ Present ☒ Absent A quorum was present.	**The DHCFP Staff Present were as follows:** Gudino, Antonio, Social Services Program Specialist III Woodrum, Homa, Senior Deputy Attorney General Flowers, Ellen, Program Officer I Young, DuAne, Deputy Administrator Olsen, David, Chief, Pharmacy Services **Managed Care Organization representatives present were as follows:** Bitton, Ryan, Health Plan of Nevada Lim, Luke, Anthem Blue Cross

Agenda Item	Record	Notes
		Beranek, Tom, SilverSummit Health Plan **Gainwell Technology Staff Present were as follows:** Leid, Jovanna, Pharm.D. **OptumRx Staff Present were as follows:** Jeffery, Carl, Pharm.D. Piccirilli, Annette Hansen, Sean **The public attendee list is included as Attachment A.** **Note**: Participants may not have chosen to reveal their identity and in the absence of a sign-in sheet the attendee list's accuracy is not assured.

Agenda Item	Record	Notes
2. General Public Comment	Dr. Jeffery announced the meeting is being recorded. A comment was made by Dr. Craig McDonald with the University of California, Davis about offering information on exon skipping drugs. Dr. McDonald explained the available studies comparing the natural progression of Duchenne Muscular Dystrophy to golodirsen treatment showing preservation of ambulation as well as upper limb strength and pulmonary strength meaning mechanical ventilation is delayed three to four years. Dr. McDonald advocated for golodirsen to be available to non-ambulatory patients with reasonable pulmonary function and upper limb function. A comment was made by Dr. McKinnon agreeing with the comments from Dr. McDonald repeating the request to have golodirsen available to non-ambulatory patients. Dr. McKinnon explained why non-ambulatory patients were excluded from the clinical trials due to confounding factors during the study design. No further public comment was offered.	
3. Administrative		
a. **<u>For Possible Action</u>**: Review and Approve Meeting Minutes from October 22, 2020	No corrections were offered. Board Member Adeolokun moved to approve the minutes as presented, and Board Member Le seconded the motion. A vote was taken, and the results were as follows from members in attendance (in favor, against, and abstentions where applicable): Jennifer Wheeler, Pharm.D., Chair: Yes ☒ No ☐ Abst. ☐ Netochi Adeolokun, Pharm.D., Vice Chair: Yes ☒ No ☐ Abst. ☐ Crystal Castaneda, MD: Yes ☒ No ☐ Abst. ☐ Dave England, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Mohammad Khan, MD: Yes ☒ No ☐ Abst. ☐ Brian Le, DO: Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record	Notes
b. Status Update by DHCFP	Mr. Antonio Gudino updated the Board regarding the scheduled public hearing on January 21, 2021, which included the changes from the past Drug Use Review Board Meeting, and welcomed the newest Board Member Dr. Crystal Castaneda and asked Board Member Castaneda to introduce herself. Board Member Castaneda introduced herself as a pediatrician at Community Health Alliance moving from Chicago to Nevada about a year ago. Deputy Young updated the Board on staffing changes within the DHCFP, Mr. Antonio Gudino was promoted to the manager of the pharmacy program and a new Pharmacy Chief will start Monday. David Olsen comes from the Division of Public and Behavioral Health and was the Quality Improvement Manager for the Chronic Disease Prevention Health Section. Chief Olsen thanked Deputy Young and commented that he is happy to be at the meeting. Deputy Young continued with updates regarding the Legislative Session and the Governor's Budget and the restoration of the rates that were expected and reductions in services with the help of President Biden's intent to continue the public health emergency and the enhanced Federal Match.	
4. Clinical Presentations		
a. **<u>For Possible Action</u>**: Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for anticonvulsants, miscellaneous.		
i. <u>Public comment</u> on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. No written comment was received. No public comment was offered.	

<table>
<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td>ii. Presentation of utilization and clinical information.</td><td>Dr. Jeffery presented information regarding Fintepla for Dravet Syndrome, pointing out there was no utilization of this medication. Dr. Jeffery reviewed Dravet Syndrome’s presentation, symptoms, onset in patients, treatment goals, and other available treatments. Dr. Jeffery highlighted two clinical trials demonstrating a significant reduction in seizure frequency in the treatment group. Dr. Jeffery outlined the proposed criteria as presented in the binder.

Dr. Bitton agreed with the presented criteria and reported no Fintepla utilization.

Dr. Lim agreed with the presented criteria and reported no Fintepla utilization.

Mr. Beranek proposed changes to the proposed criteria to require at least one other anticonvulsant and reported no Fintepla utilization.</td><td></td></tr>
<tr><td>iii. Discussion by Board and review of utilization data.</td><td>Board Member England commented he would support adding a minimum age of two years.</td><td></td></tr>
<tr><td>iv. Proposed adoption of updated prior authorization criteria.</td><td>Board Member Adeolokun moved to accept the proposed criteria with the addition of a minimum age of two years, and Board Member England seconded.

A vote was held:

<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Jennifer Wheeler, Pharm.D., Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Netochi Adeolokun, Pharm.D., Vice Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Crystal Castaneda, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Dave England, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Mohammad Khan, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Brian Le, DO</td><td>☒</td><td>☐</td><td>☐</td></tr>
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<tr><td>b. <u>For Possible Action</u>: Discussion and possible</td><td></td><td></td></tr>
</table>

Agenda Item	Record	Notes
adoption of updated prior authorization criteria and/or quantity limits for agents used in the treatment of Spinal Muscular Atrophy (SMA).		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. No written comment was received. No public comment was offered.	
ii. Presentation of utilization and clinical information.	Dr. Jeffery presented information on Evrysdi or risdiplam for the treatment of spinal muscular atrophy. Dr. Jeffery reviewed the symptoms, presentation, progression, classification, and outcomes of spinal muscular atrophy. Dr. Jeffery reported no utilization of Evrysdi. Dr. Jeffery highlighted the two available clinical trials demonstrating Evrysdi treatment leading to clinically meaningful outcomes. Dr. Jeffery outlined the proposed criteria. Dr. Bitton agreed with the presented criteria and reported no Evrysdi utilization. Dr. Lim agreed with the presented criteria and reported no Evrysdi utilization. Mr. Beranek agreed with the presented criteria and reported no Evrysdi utilization.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members. No comments were made.	
iv. Proposed adoption of updated prior	Board Member Adeolokun moved to accept the criteria as presented, and Board Member Castaneda seconded the motion. A vote was held:	

Agenda Item	Record				Notes
authorization criteria.		Yes	No	Abst.	
	Jennifer Wheeler, Pharm.D., Chair	☒	☐	☐	
	Netochi Adeolokun, Pharm.D., Vice Chair	☒	☐	☐	
	Crystal Castaneda, MD	☒	☐	☐	
	Dave England, Pharm.D.	☒	☐	☐	
	Mohammad Khan, MD	☒	☐	☐	
	Brian Le, DO	☒	☐	☐	
c. **For Possible Action**: Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for agents used in the treatment of Duchenne Muscular Dystrophy (DMD).					
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. Comment was offered by Tracy Copeland with Sarepta Therapeutics referencing testimony provided by Drs. McDonald and McKinnon and pointed out the package insert does not list an age restriction or ambulation requirement. Comment was offered by Kelly Maynard on behalf of a patient advocacy organization for Duchenne Muscular Dystrophy advocating for removing an ambulatory requirement because it is not listed in the FDA approved label. The following written public comment is attached hereto: 1. A letter dated January 16, 2021, from the Parent Project Muscular Dystrophy advocating for access to Vyondys 53. The public comment referenced above was highlighted on the record for members of the Board by Dr. Jeffery.				

Agenda Item	Record	Notes
	No further public comment was offered.	
ii. Presentation of utilization and clinical information.	Dr. Jeffery commented the discussion will only include Vyondys 53, Viltepso will be included in a future agenda. Dr. Jeffery presented information on Duchenne's Muscular Dystrophy, including the presentation, cause, symptoms, and outcomes. Dr. Jeffery highlighted the normal administration, the one available study demonstrating efficacy, and the proposed criteria. Dr. Jeffery reported no utilization of Vyondys 53. Dr. Bitton agreed with the presented criteria and reported no Vyondys 53 utilization. Dr. Lim agreed with the presented criteria and reported no Vyondys 53 utilization. Mr. Beranek recommended including requirements for ambulatory function, stable cardiac function, stable pulmonary function, and is prescribed with an oral corticosteroid. Mr. Beranek reported no Vyondys 53 utilization.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked if the age on the proposed criteria comes from the clinical trial data. Dr. Jeffery replied the trials started with patients age six years and older. Chairwoman Wheeler commented the normal onset is at age four years and expressed concern about limiting access for younger members who may benefit. Board Member England commented the age is not listed in the package insert, so should not be included in the criteria. Board Member Castaneda agreed with reducing the age requirement. Board Member Adeolokun asked why the ambulation requirement is in the criteria. Dr. Jeffery replied with information in the original study was in ambulatory patients.	Public comment from Kelly Maynard was taken out of order owing to the full remote nature of the meeting and accommodation of public comment on the new (for DUR purposes) Microsoft Teams platform.

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<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td></td><td>Board Member Castaneda agreed with removing the ambulatory requirement.

Board Member England asked if the six-minute walk test was removed, what criteria would be used to measure outcomes.

Dr. Jeffery offered information on other criteria asking for the clinician’s opinion on treatment efficacy.

Chairwoman Wheeler offered that quality of life should be determined on a patient-by-patient basis.</td><td></td></tr>
<tr><td>iv. Proposed adoption of updated prior authorization criteria.</td><td>Chairwoman Wheeler suggested removing the age requirement entirely from the proposed criteria and removing the documentation requirement that the patient is ambulatory via the six-minute walk test from the initial authorization and reauthorization criteria.

Board Member England agreed and moved to accept the modified criteria.

Dr. Leid asked for clarification around not using the FDA approved age and impact on policy if it is not listed in the criteria.

Dr. Jeffery confirmed the FDA approved indication does not include an age.

Board Member Castaneda seconded the motion.

A vote was held:

<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Jennifer Wheeler, Pharm.D., Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Netochi Adeolokun, Pharm.D., Vice Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
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<tr><td>Brian Le, DO</td><td>☒</td><td>☐</td><td>☐</td></tr>
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</td><td></td></tr>
<tr><td>d. <u>For Possible Action</u>: Discussion and possible adoption of prior authorization criteria</td><td></td><td></td></tr>
</table>

Agenda Item	Record	Notes
and/or quantity limits for topical neuropathic pain agents.		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. No written comment was received. No public comment was offered.	
ii. Presentation of utilization and clinical information.	Dr. Jeffery highlighted Qutenza clinical information including indication, clinical trials demonstrating Qutenza offered a greater reduction in pain compared to the control group and discussed other common treatments for neuropathic pain. Dr. Jeffery reported no utilization of Qutenza and presented the proposed criteria. Dr. Bitton agreed with the presented criteria and reported no Qutenza utilization. Dr. Lim agreed with the presented criteria and reported no Qutenza utilization. Mr. Beranek agreed with the presented criteria and reported no Qutenza utilization.	
iii. Discussion by Board and review of utilization data.	Board Member England asked for clarification for the three-month interval and if there is a way to stop members from using over the counter capsaicin in between. Dr. Jeffery offered information to clarify that the three-month limit is due to the over-stimulation of the nerve cells due to the higher concentration compared to the over the counter medication.	
iv. Proposed adoption of updated prior authorization criteria.	Board Member Adeolokun moved to accept the criteria as presented, and Board Member Castaneda seconded the motion. A vote was held: Jennifer Wheeler, Pharm.D., Chair — Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record	Notes
	Netochi Adeolokun, Pharm.D., Vice Chair ☒ ☐ ☐ Crystal Castaneda, MD ☒ ☐ ☐ Dave England, Pharm.D. ☒ ☐ ☐ Mohammad Khan, MD ☒ ☐ ☐ Brian Le, DO ☒ ☐ ☐	
5. DUR Board Requested Reports		
a. **For Possible Action**: Opioid utilization – top prescribers and members		
i. Discussion by the Board and review of utilization data.	Dr. Jeffery presented the opioid utilization report identifying a downward trend in the count of claims, morphine equivalent dose, and total morphine equivalent dose per day supply. Dr. Jeffery highlighted the top ten members by morphine equivalent dose report calling out the common use of long-acting and short-acting opioids for pain management. Dr. Jeffery discussed the top ten prescribers sorted by total morphine equivalent dose and total morphine equivalent dose per member and per day supply. Dr. Jeffery identified the prescriber listed as a hospitalist is also listed as internal medicine where the rest of the specialties lean toward pain management and mid-level practitioners who frequently handle the refills of opioids. Board Member Le asked about the prescriber listed as a student. Dr. Jeffery replied he will investigate the prescriber and provide details at a future meeting. Dr. Bitton discussed the opioid utilization detailing the flat utilization for total morphine equivalent dose utilization over time, the trend for prescribers in the top ten by morphine equivalent dose over the two quarters, and the top members by morphine equivalent dose with a comparison to the top opioid prescribers. Dr. Lim discussed the opioid utilization detailing the slight increase in claim count in the second quarter but decreased in the third quarter, highlighted the bump in total morphine equivalent dose in April and May, and detailed the top 10 prescribers and members reports.	

Agenda Item	Record	Notes
	Mr. Beranek discussed the opioid utilization calling out the uptick in morphine equivalent dose recently and a new prescriber on the top ten prescriber list recently certified to prescribe buprenorphine driving up the claim counts. No further discussion from the Board.	
ii. Requests for further evaluation or proposed clinical criteria to be presented at a later date.	The Board made no requests.	
6. Standard DUR Reports		
a. Review of Prescribing/Program Trends.		
i. Top 10 Therapeutic Classes for Q2 2020 and Q3 2020 (by Payment and by Claims).	Dr. Jeffery explained the top ten therapeutic class report highlighting the anticonvulsant class and sympathomimetics at the top by claim count and antihemophilic and HIV treatment by total spend in the class. Dr. Jeffery identified the challenge of managing the HIV class with the Nevada Revised Statues limiting any utilization management. Dr. Bitton described the reports including HIV and rheumatoid arthritis treatments are at the top of the pharmacy paid amount while antihemophilic treatment is filled under the medical benefit and does not show on the pharmacy claim information. Dr. Lim highlighted the top claims area by paid amount with Biktarvy trends increasing without taking claims from other treatments within the class and commented on the usual therapies with diabetes and behavioral health. Mr. Beranek outlined antiretroviral utilization is similar to the use of Biktarvy, but the utilization is consistent over the quarters.	

Agenda Item	Record	Notes
b. Concurrent Drug Utilization Review (ProDUR).		
i. Review of Q3 2020. ii. Review of Top Encounters by Problem Type.	Dr. Jeffery explained the concurrent drug utilization review report highlighting drug-drug interactions and duplicate therapies are the top interventions. Dr. Bitton highlighted the concurrent drug use review edits and commented they are similar to the other programs. Dr. Lim identified similar trends with concurrent drug use review with therapeutic duplications and high dose edits being the top. Mr. Beranek described the concurrent drug use review report and commented that therapeutic duplication and early refills are the top alerts for SilverSummit.	
c. Retrospective Drug Utilization Review (RetroDUR).		
i. Status of previous quarter. ii. Status of current quarter. iii. Review and discussion of responses.	Dr. Jeffery discussed initiatives for the SUPPORT Act with combinations of opioids with antipsychotics and opioids with benzodiazepines and a survey asking for provider feedback on continuous glucose monitors. Dr. Bitton highlighted a few pages of retrospective drug use review reports including duplicate therapy, gaps in care for cardiovascular issues, sickle cell disease, and COPD. Mr. Beranek described the retrospective drug use review initiatives with the focus on non-adherent patients using medication for hypertension and respiratory issues and reported a good response rate to the initiatives.	
7. Closing Discussion		
a. Public Comment	Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.	

Agenda Item	Record	Notes
b. **For Possible Action**: Data and Location of the next meeting	Chairwoman Wheeler stated the next meeting is scheduled for April 22, 2021, and will be held virtually.	
c. Adjournment	The meeting was adjourned at 2:50 p.m.	

Attachment A – Member of the Public in Attendance

Adams, Jill
Bala, Kaysen
Booth, Robert
Colabianchi, Jeana
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Maynard, Kelly
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Nelson, Ann
Omega, Duveneck
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Attachment B – Submitted Written Comment

Parent Project
Muscular Dystrophy

Clinical Presentations

Prior Authorization Guideline

Guideline Name Multiple Sclerosis Agents

1 . Criteria

Product Name: Aubagio (teriflunomide), Gilenya (fingolimod), Brand Tecfidera ,Generic dimethyl fumarate, Avonex (interferon beta-1a), Avonex Admin Pack, Betaseron (interferon beta-1b), Brand Copaxone, Extavia (interferon beta-1b), Rebif (interferon beta-1a), Tysabri (natalizumab), Generic dalfampridine, Generic glatopa, Generic glatiramer, Bafiertam (monomethyl fumarate), Mayzent (siponimod fumarate), Vumerity (diroximel fumarate), Plegridy (peginterferon beta-1a), Kesimpta	
Approval Length	12 month(s)
Guideline Type	Prior Authorization
Approval Criteria **1** - Diagnosis of Multiple Sclerosis	

Product Name: Brand Ampyra, Generic dalfampridine	
Approval Length	3 Months for Initial Authorization, 12 Months for Reauthorization
Guideline Type	Prior Authorization
Approval Criteria **1** - Diagnosis of Multiple Sclerosis **AND**	

2 - Recipient is not pregnant or attempting to conceive

AND

3 - Recipient does not have a history of seizures

AND

4 - Recipient does not have moderate to severe renal dysfunction (creatine clearance less than or equal to 50 mL/min)

AND

5 - Medication is being used to improve the recipient's walking speed

AND

6 - Medication is being prescribed by or in consultation with a neurologist

AND

7 - The recipient is ambulatory and has an EDSS score between 2.5 and 6.5

Product Name: Lemtrada (alemtuzumab)	
Approval Length	12 month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of a relapsing form of Multiple Sclerosis (e.g., relapsing-remitting MS, secondary-progressive MS with relapses)

AND

2 - One of the following:

2.1 Both of the following:

2.1.1 The recipient has not been previously treated with alemtuzumab

AND

2.1.2 The recipient has had failure after a trial of at least four weeks; a contraindication, or intolerance to two of the following disease-modifying therapies for MS:

- Aubagio (teriflunomide)
- Avonex (interferon beta-1a)
- Betaseron (interferon beta-1b)
- Copaxone/Glatopa (glatiramer acetate)
- Extavia (interferon beta-1b)
- Gilenya (fingolimod)
- Mavenclad (cladribine)
- Mayzent (siponimod)
- Ocrevus (ocrelizumab)
- Plegridy (peginterferon beta-1a)
- Rebif (interferon beta-1a)
- Tecfidera (dimethyl fumarate)
- Tysabri (natalizumab)

OR

2.2 Both of the following:

2.2.1 The recipient has previously received treatment with alemtuzumab

AND

2.2.2 The recipient has had at least 12 months elapsed or will have elapsed since the most recent treatment course with alemtuzumab

AND

3 - The medication will not be used in combination with another disease-modifying therapy for MS

Product Name: Mavenclad (cladribine)	
Approval Length	1 month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of a relapsing form of Multiple Sclerosis (e.g., relapsing-remitting MS, secondary-progressive MS with relapses)

AND

2 - One of the following:

2.1 Both of the following:

2.1.1 The recipient has not been previously treated with cladribine

AND

2.1.2 The recipient has had failure after a trial of at least four weeks; a contraindication, or intolerance to two of the following disease-modifying therapies for MS:

- Aubagio (teriflunomide)
- Avonex (interferon beta-1a)
- Betaseron (interferon beta-1b)
- Copaxone/Glatopa (glatiramer acetate)
- Extavia (interferon beta-1b)
- Gilenya (fingolimod)
- Lemtrada (alemtuzumab)
- Mayzent (siponimod)
- Ocrevus (ocrelizumab)
- Plegridy (peginterferon beta-1a)
- Rebif (interferon beta-1a)
- Tecfidera (dimethyl fumarate)
- Tysabri (natalizumab)

OR

2.2 Both of the following:

2.2.1 The recipient has previously received treatment with cladribine

AND

2.2.2 The recipient has not already received the FDA-recommended lifetime limit of two treatment courses (or four treatment cycles total) of cladribine

AND

3 - The medication will not be used in combination with another disease-modifying therapy for MS

Product Name: Ocrevus (ocrelizumab)	
Approval Length	12 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of a relapsing form of Multiple Sclerosis (e.g., relapsing-remitting MS, secondary-progressive MS with relapses) or diagnosis of Primary Progressive Forms of Multiple Sclerosis (PPMS)

AND

2 - The medication must not be used in combination with another disease-modifying therapy for MS

AND

3 - The medication must not be used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra])

AND

4 - The medication must not be used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone)

Product Name: Ocrevus (ocrelizumab)	
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Documentation of a positive clinical response to Ocrevus therapy

AND

2 - The medication must not be used in combination with another disease-modifying therapy for MS

AND

3 - The medication must not be used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra])

AND

4 - The medication must not be used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone)

Product Name: Zeposia (ozanimod)	
Approval Length	12 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of a relapsing form of Multiple Sclerosis (e.g., relapsing-remitting MS, secondary-progressive MS with relapses)

AND

2 - The medication is prescribed by or in consultation with a neurologist

AND

3 - One of the following:

3.1 The agent is used for continuation of therapy

OR

3.2 The recipient has had failure after a trial of at least 4 weeks, contraindication, or intolerance to at least two of the following disease-modifying therapies for MS:

- Avonex (interferon beta-1a)
- Betaseron (interferon beta-1b)
- Copaxone/Glatopa (glatiramer acetate)
- Tecfidera (dimethyl fumarate)

Product Name: Zeposia (ozanimod)	
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient has documentation of positive clinical response to therapy (e.g., improvement in radiologic disease activity, clinical relapses, disease progression)

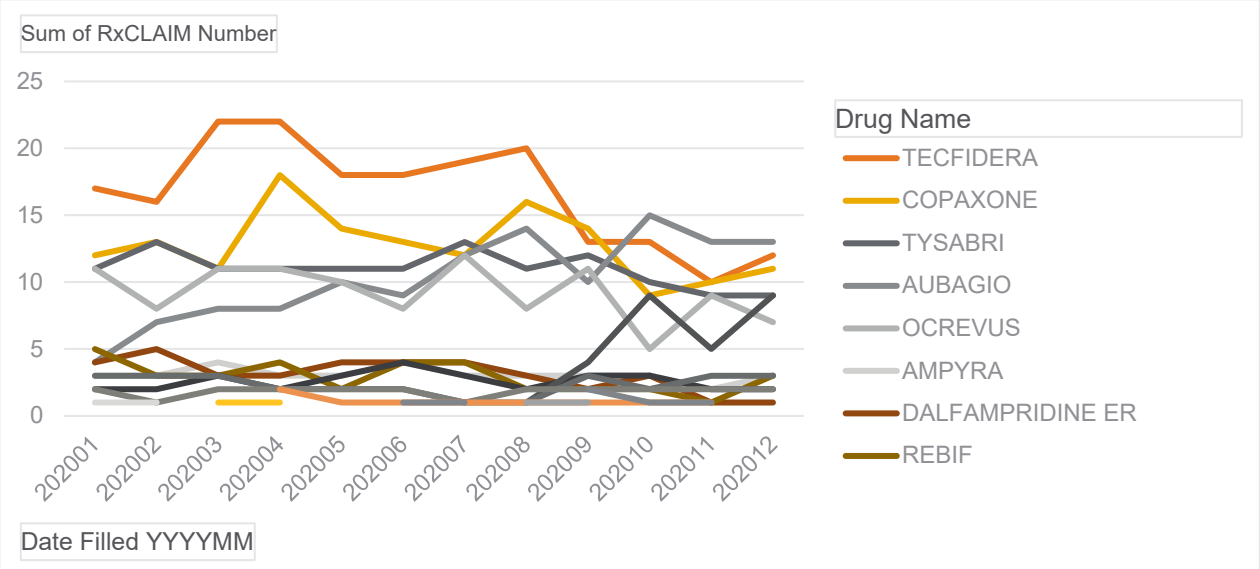
AND

2 - The medication is prescribed by or in consultation with a neurologist

Nevada Medicaid

Multiple Sclerosis Agents
Fee for Service
January 1, 2020 – December 31, 2020

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
AMPYRA	4	37	1,110	2,220
AUBAGIO	23	123	4,150	4,360
AVONEX	2	22	616	22
AVONEX PEN	3	31	868	31
BETASERON	1	2	56	28
COPAXONE	16	153	4,384	2,736
DALFAMPRIDINE ER	6	37	1,110	2,220
DIMETHYL FUMARATE	11	28	817	1,634
GILENYA	4	28	840	840
GLATIRAMER ACETATE	2	3	144	60
GLATOPA	1	4	296	120
KESIMPTA	1	1	28	1
MAVENCLAD	3	6	230	50
MAYZENT	1	1	30	30
OCREVUS	62	111	1,219	62,360
PLEGRIDY	1	9	252	9
REBIF	4	35	960	210
REBIF REBIDOSE	1	5	140	30
TECFIDERA	31	200	6,120	12,240
TECFIDERA STARTER PACI	6	6	180	360
TYSABRI	17	132	896	1,980



CC. Multiple Sclerosis (MS) Agents

Therapeutic Class: Agents for the treatment of Neuromuscular Transmission Disorder
Last Reviewed by the DUR Board: January 23, 2020

MS Agents aresubject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Ampyria® (dalfampridine)

   a. Approval will be given if all the following criteria are met and documented:

      1. The recipient must have a diagnosis of MS; and

      2. The medication is being used to improve the recipient's walking speed; and

      3. The medication is being prescribed by or in consultation with a neurologist; and

      4. The recipient is ambulatory and has an EDSS score between 2.5 and 6.5; and

      5. The recipient does not have moderate to severe renal dysfunction (CrCL >50 ml/min); and

      6. The recipient does not have a history of seizures; and

      7. The recipient is not currently pregnant or attempting to conceive.

   b. Prior Authorization Guidelines

      1. Initial prior authorization approval will be for three months.

      2. Request for continuation of therapy will be approved for one year.

2. Relapsing Forms of MS Agents:

   a. Approval will be given if all the following criteria are met and documented:

      1. The recipient must have a diagnosis of a relapsing form of MS (e.g., relapsing-remitting MS, secondary-progressive MS with relapses).

   b. Lemtrada® (alemtuzumab)

      1. Approval will be given if all the following criteria are met and documented:

a. The recipient must have a diagnosis of a relapsing form of MS; and one of the following:

1. Both the following:

a. The recipient has not been previously treated with alemtuzumab; and

b. The recipient has had failure after a trial of at least four weeks; a contraindication or intolerance to two of the following disease-modifying therapies for MS:

1. Aubagio (teriflunomide)

2. Avonex (interferon beta-1a)

3. Betaseron (interferon beta-1b)

4. Copaxone/Glatopa (glatiramer acetate)

5. Extavia (interferon beta-1b)

6. Gilenya (fingolimod)

7. Lemtrada (alemtuzumab

8. Mayzent (siponimod)

9. Ocrevus (ocrelizumab)

10. Plegridy (peginterferon beta-1a)

11. Rebif (interferon beta-1a)

12. Tecfidera (dimethyl fumarate)

13. Tysabri (natalizumab); or

2. Both the following:

a. The recipient has previously received treatment with alemtuzumab; and

b. The recipient has had at least 12 months elapsed or will have elapsed since the most recent treatment course with alemtuzumab; and

3. The medication will not be used in combination with another disease-modifying therapy for MS.

2. Prior Authorization Guidelines

a. Initial authorization approval will be for 12 months.

b. Recertification approval will be for 12 months.

c. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

c. Mavenclad® (cladribine)

1. Approval will be given if all the following criteria are met and documented:

a. The recipient must have a diagnosis of a relapsing form of MS (e.g., relapsing-remitting MS, secondary-progressive MS with relapses); and one of the following:

1. Both the following:

a. The recipient has not been previously treated with cladribine; and

b. The recipient has had failure after a trial of at least four weeks; contraindication, or intolerance to two of the following disease-modifying therapies for MS:

1. Aubagio (teriflunomide

2. Avonex (interferon beta-1a)

3. Betaseron (interferon beta-1b)

4. Copaxone/Glatopa (glatiramer acetate)

5. Extavia (interferon beta-1b)

6. Gilenya (fingolimod)

7. Lemtrada (alemtuzumab)

8. Mayzent (siponimod)

9. Ocrevus (ocrelizumab)

10. Plegridy (peginterferon beta-1a)

11. Rebif (interferon beta-1a)

12. Tecfidera (dimethyl fumarate)

13. Tysabri (natalizumab); or

2. Both the following:

a. The recipient has previously received treatment with cladribine; and

b. The recipient has not already received the FDA-recommended lifetime limit of two treatment courses (or four treatment cycles total) of cladribine; and

b. The medication will not be used in combination with another disease-modifying therapy for MS.

2. Prior Authorization Guidelines

a. Prior authorization approval will be for one month.

b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

d. Ocrevus® (ocrelizumab)

1. Approval will be given if all the following criteria are met and documented:

a. The recipient has a diagnosis of a relapsing form of MS (e.g., relapsing-remitting MS, secondary-progressive MS with relapses); and

b. The medication must not be used in combination with another disease-modifying therapy for MS; and

c. The medication must not be used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra]); and

d. The medication must not be used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone).

2. Recertification Request (the recipient must meet all criteria):

a. Documentation of a positive clinical response to Ocrevus® therapy; and

b. The medication must not be used in combination with another disease-modifying therapy for MS; and

c. The medication must not be used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra]); and

d. The medication must not be used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone).

3. Prior Authorization Guidelines

a. Initial prior authorization approval will be 12 months.

b. Recertification approval will be for 12 months.

c. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

3. Primary Progressive Forms of Multiple Sclerosis (PPMS) Agents:

a. Ocrevus® (ocrelizumab)

1. Approval will be given if all the following criteria are met and documented:

a. The recipient must have a diagnosis of PPMS; and

b. The medication must not be used in combination with another disease-modifying therapy for MS; and

c. The medication must not be used in combination with another B-cell targeted therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra]); and

d. The medication must not be used in combination with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone).

2. Recertification Request (the recipient must meet all criteria):

a. Documentation of a positive clinical response to Ocrevus® therapy; and

b. The medication must not be used in combination with another disease-modifying therapy for MS; and

c. The medication must not be used in combination with another B-cell target therapy (e.g., rituximab [Rituxan], belimumab [Benlysta], ofatumumab [Arzerra]); and

d. The medication must not be used with another lymphocyte trafficking blocker (e.g., alemtuzumab [Lemtrada], mitoxantrone).

3. Prior Authorization Guidelines

a. Initial prior authorization approval will be for 12 months.

b. Recertification approval will be for 12 months.

c. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

INTRODUCTION

- Multiple Sclerosis (MS), a chronic, immune-mediated disease of the central nervous system (CNS), is among the most common causes of neurological disability in young adults *(MS Coalition 2019, National Institutes of Health MS 2019)*. Multiple sclerosis is characterized by inflammation, demyelination, and degenerative changes in the CNS. Most patients with MS experience relapses and remissions of neurological symptoms, usually early in the disease process, with clinical events that are generally associated with CNS inflammation. There are 4 clinical subtypes of MS:
  - Relapsing-remitting MS (RRMS), which is characterized by acute attacks followed by partial or full recovery. This is the most common form of MS, accounting for an estimated 85% of cases.
  - Secondary progressive MS (SPMS) begins as RRMS; however, the attack rate declines over time. Patients experience a gradual deterioration. Patients with RRMS for more than 10 years may transition to SPMS.
  - Primary progressive MS (PPMS) occurs in approximately 15% of patients with MS. Patients have a continuous and gradual decline in function without evidence of acute attacks.
  - Clinically isolated syndrome (CIS) refers to the first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation or demyelination in the CNS. Patients who experience a CIS may or may not develop MS *(Sanvito et al 2011, National MS Society 2020[a])*.
- A revision of the MS clinical course descriptions recommended that the core MS phenotype descriptions of relapsing and progressive disease be retained with some of the following modifications: (1) an important modifier of these core phenotypes is an assessment of disease activity, as defined by clinical assessment of relapse occurrence or lesion activity detected by CNS imaging; (2) the second important modifier of these phenotypes is a determination of whether progression of disability has occurred over a given time period; and (3) the historical category of progressive-relapsing multiples sclerosis (PRMS) can be eliminated since subjects so categorized would now be classified as PPMS patients with disease activity *(Lublin et al 2014)*.
- An estimated 1 million adults in the United States are affected by MS. Most patients are diagnosed between the ages of 20 and 50 years, and MS is at least 2 to 3 times more common in women than in men *(National MS Society 2020[b])*.
- Diagnosis of MS requires evidence that demonstrates lesions in the CNS showing “dissemination in space” (ie, suggestions of damage in > 1 place in the nervous system) and “dissemination in time” (ie, suggestions that damage has occurred more than once). It is a diagnosis of exclusion, after consideration of and elimination of more likely diagnoses *(Thompson et al 2018)*.
- The patient evaluation includes an extensive history, neurological examination, laboratory tests to rule out other possible causes, magnetic resonance imaging (MRI) to evaluate for new disease and signs of more chronic damage, and possibly lumbar puncture (*Thompson et al 2018*).
- Exacerbations, also known as flares, relapses, or attacks of MS are caused by inflammation in the CNS that lead to damage to the myelin and slowing or blocking of transmission of nerve impulses. A true MS exacerbation must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. Exacerbations can be mild or severe. Intravenous (IV) corticosteroids may be used to treat severe exacerbations of MS. Corticosteroids decrease acute inflammation in the CNS but do not provide any long-term benefits *(Frohman et al 2007)*.
- The approach to treating MS includes the management of symptoms, treatment of acute relapses, and utilization of disease-modifying therapies (DMTs) to reduce the frequency and severity of relapses, reduce lesions on MRI scans, and possibly delay disease and disability progression *(Rae-Grant et al 2018)*. The American Academy of Neurology (AAN), the European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) guidelines recommend initiation of DMTs early on in the patient’s disease course (*Montalban et al 2018, Rae-Grant et al 2018*). These therapies may delay the progression from CIS to clinically definite MS (CDMS) *(Armoiry et al 2018, Miller et al 2012)*. The MS Coalition, the AAN, and the Association of British Neurologists guidelines support access to available DMTs for patients with MS. While there are no precise algorithms to determine the order of product selection, therapy should be individualized and patients’ clinical response and tolerability to medications should be monitored (*MS Coalition 2019, Rae-Grant et al 2018, Scolding et al 2015*).

- Pediatric-onset MS is rare, with the vast majority of cases demonstrating a relapsing-remitting disease course (*Otallah et al 2018*). Gilenya (fingolimod) is the first FDA-approved agent for pediatric patients. Its approval was based on the PARADIGMS trial (*Chitnis et al 2018*).
- Vumerity (diroximel fumarate), is rapidly converted to monomethyl fumarate (MMF), which also is the active metabolite of Tecfidera (dimethyl fumarate). Diroximel fumarate may offer improved gastrointestinal (GI) tolerability as compared to dimethyl fumarate (*Naismith et al 2019, Selmaj et al 2019*). In April 2020, the FDA approved another agent in this class, Bafiertam (monomethyl fumarate). This drug is considered a "bioequivalent alternative" to dimethyl fumarate since dimethyl fumarate is a prodrug, and monomethyl fumarate is its active ingredient. Since the drug is already in its active form, it is administered at a lower dose than dimethyl fumarate, and it is thought that it may lead to fewer GI adverse effects (*Bafiertam prescribing information 2020*).
- All agents in this class review are listed as Multiple Sclerosis Agents in Medispan; the exceptions are mitoxantrone (listed as an antineoplastic antibiotic) and Ampyra (dalfampridine) (listed as a potassium channel blocker).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Ampyra (dalfampridine)	✔
Aubagio (teriflunomide)	✔ *
Avonex (interferon β-1a)	-
Bafiertam (monomethyl fumarate)	-
Betaseron (interferon β-1b)	-
Copaxone, Glatopa† (glatiramer acetate)	✔
Extavia (interferon β-1b)	-
Gilenya (fingolimod)	✔ *
Kesimpta (ofatumumab)§	-
Lemtrada (alemtuzumab)	-
Mavenclad (cladribine)‖	-
Mayzent (siponimod)	-
mitoxantrone	✔ ‡
Ocrevus (ocrelizumab)	-
Plegridy (peginterferon β-1a)	-
Rebif (interferon β-1a)	-
Tecfidera (dimethyl fumarate)	✔
Tysabri (natalizumab)	-
Vumerity (diroximel fumarate)	-
Zeposia (ozanimod)	-

*Generics have received FDA-approval; however, settlement agreements will delay launch.
†Glatopa by Sandoz is an FDA-approved generic for Copaxone (glatiramer acetate).
‡Although brand Novantrone has been discontinued, generic mitoxantrone remains available.
§Ofatumumab was originally approved as an IV formulation for treatment of chronic lymphocytic leukemia as a different product (Arzerra). Only clinical data for ofatumumab use in MS are included in this review.
‖Cladribine injection is indicated for the treatment of active hairy-cell leukemia. This oncology indication is not related to the treatment of MS and will not be discussed in this review.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Improve walking in MS	Relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults	Relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease in adults	Primary Progressive MS in adults	Reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary progressive, progressive relapsing, or worsening relapsing-remitting MS
Ampyra (dalfampridine)	✔ *	-	-	-	-
Aubagio (teriflunomide)	-	✔	-	-	-
Avonex (interferon β-1a)	-	✔	-	-	-
Bafiertam (monomethyl fumarate)	-	✔	-	-	-
Betaseron/Extavia (interferon β-1b)	-	✔	-	-	-
Copaxone (glatiramer acetate)	-	✔	-	-	-
Gilenya (fingolimod)	-	✔ †	-	-	-
Kesimpta (ofatumumab)		✔			
Lemtrada (alemtuzumab)	-	-	✔ ‡	-	-
Mavenclad (cladribine)	-	-	✔ §	-	-
Mayzent (siponimod)	-	✔	-	-	-
mitoxantrone	-	-	-	-	✔ ‖
Ocrevus (ocrelizumab)	-	✔	-	✔	-
Plegridy (peginterferon β-1a)	-	✔	-	-	-
Rebif (interferon β-1a)	-	✔	-	-	-
Tecfidera (dimethyl fumarate)	-	✔	-	-	-
Tysabri (natalizumab)	-	✔ ¶	-	-	-
Vumerity (diroximel fumarate)	-	✔	-	-	-
Zeposia (ozanimod)	-	✔	-	-	-

*Ampyra is indicated as a treatment to improve walking in adult patients with MS. This was demonstrated by an increase in walking speed.
†Approved in patients 10 years of age and older.
‡Because of its safety profile, Lemtrada should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS. Lemtrada is not recommended for use in patients with CIS because of its safety profile.
§ Because of its safety profile, use of Mavenclad is generally recommended for patients who have had an inadequate response, or are unable to tolerate, an alternate drug indicated for the treatment of MS. Mavenclad is not recommended for use in patients with CIS because of its safety profile.
‖Mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening RRMS (ie, patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated for the treatment of patients with PPMS. The product has additionally been approved for several cancer indications including pain related to advanced hormone-refractory prostate cancer and initial therapy of acute nonlymphocytic leukemia (includes myelogenous, promyelocytic, monocytic, and erythroid acute leukemias).
¶ Tysabri increases the risk of Progressive Multifocal Leukoencephalopathy (PML). When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. Tysabri is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who

have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. In CD, Tysabri should not be used in combination with immunosuppressants or inhibitors of TNF-α.

(Prescribing information: Ampyra 2019, Aubagio 2020, Avonex 2020, Bafiertam 2020, Betaseron 2020, Copaxone 2020, Extavia 2020, Gilenya 2019, Glatopa 2020, Kesimpta 2020, Lemtrada 2020, Mavenclad 2019, Mayzent 2019, mitoxantrone 2018, Ocrevus 2020, Plegridy 2021, Rebif 2020, Tecfidera 2020, Tysabri 2020, Vumerity 2020, Zeposia 2020)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- In the management of MS, numerous clinical trials have established the safety and efficacy of the DMTs in reducing the frequency of relapses, lesions on MRI scans, and possibly delaying disability progression.

Interferons and glatiramer acetate

- Pivotal clinical trials demonstrating efficacy in reducing the rate of relapses, burden of disease on MRI, and disability progression for the interferons (IFNs) and glatiramer acetate were published in the 1990's *(Jacobs et al 1996, Johnson et al 1995, The interferon beta [IFNβ] Multiple Sclerosis Study Group 1993, The IFNβ Multiple Sclerosis Study Group 1995)*. Long-term follow-up data for IFN β-1b show that overall survival in MS is improved *(Goodin et al 2012)*.
- Head-to-head trials have found Copaxone (glatiramer acetate), Rebif (IFNβ-1a SC), and Betaseron (IFNβ-1b) to be comparable in terms of relapse rate reduction and disease and disability progression *(PRISMS 1998, Kappos et al 2006, Mikol et al 2008, Flechter et al 2002, Cadavid et al 2009, O'Connor et al 2009)*. Results from several studies suggest that lower dose Avonex (IFNβ-1a 30 mcg IM once weekly) may be less efficacious while being more tolerable compared to Rebif (IFNβ-1a SC 3 times weekly) or Betaseron (IFNβ-1b every other day) or glatiramer acetate *(Barbero et al 2006, Durelli et al 2002, Khan et al 2001[a, b], Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*.
- In a meta-analysis of 5 randomized controlled trials (RCTs) comparing IFNs with glatiramer acetate, there were no significant differences between IFNs and glatiramer acetate in terms of the number of patients with relapses, confirmed progression, or discontinuation due to adverse events at 24 months *(La Mantia et al 2016)*.
  - At 36 months, however, evidence from a single study suggested that relapse rates were higher in the group given IFNs than in the glatiramer acetate group (risk ratio [RR] 1.40, 95% confidence interval [CI], 1.13 to 1.74; p = 0.002). While a MRI outcomes analysis showed that effects on newer enlarging T2 or new contrast-enhancing T1 lesions at 24 months were similar, the reduction in T2- and T1-weighted lesion volume was significantly greater in the groups given IFNs than in the glatiramer acetate groups (mean difference [MD] −0.58, 95% CI, −0.99 to −0.18; p = 0.004, and MD −0.20, 95% CI, −0.33 to −0.07; p = 0.003, respectively).
- In a network meta-analysis of 24 studies comparing IFNs and glatiramer acetate, both drugs were found to reduce the annualized relapse rate (ARR) as compared to placebo but did not differ statistically from each other (*Melendez-Torres et al 2018*). Ranking of the drugs based on SUCRA (surface under the cumulative ranking curve) indicated that glatiramer acetate 20 mg once daily had the highest probability for superiority, followed by peginterferon β-1a 125 mcg SC every 2 weeks.
- A meta-analysis of 6 placebo-controlled trials failed to find a significant advantage of Avonex (IFNβ-1a) 30 mcg IM once weekly compared to placebo in the number of relapse-free patients after 1 year of therapy (*Freedman et al 2008*). In contrast, other studies found Avonex (IFNβ-1a) 30 mcg IM once weekly to be comparable to the other IFNβ products in terms of relapse rate reduction, disability progression, and SPMS development *(Carra et al 2008, Limmroth et al 2007, Minagara et al 2008, Rio et al 2005, Trojano et al 2003, Trojano et al 2007)*. Moreover, IFN therapy, especially the higher dose products, is associated with the production of neutralizing antibodies (NAb), which may result in decreased radiographic and clinical effectiveness of treatment *(Goodin et al 2007, Sorensen et al 2005)*. Exploratory post-hoc analyses of the PRISMS trial linked the development of NAb with reduced efficacy *(Alsop et al 2005)*. Development of NAb among patients (N = 368) randomized to receive Rebif (IFNβ-1a) 44 or 22 mcg SC 3 times weekly for 4 years was associated with higher relapse rates (adjusted relapse rate ratio, 1.41; 95% CI, 1.12 to 1.78; p = 0.004), a greater number of active lesions, and percentage change in T2 lesion burden from baseline on MRI scan (p < 0.001).

- In a systematic review of 40 studies of MS agents including IFNβ-1a and IFNβ-1b, the primary outcome measure was the frequency of IFN NAb *(Govindappa et al 2015)*. NAb development was most frequent with IFN β-1b, followed by IFN β-1a SC, and lowest with IFN β-1a IM. Higher doses were associated with a higher rate of NAb development.
- The CombiRx trial evaluated the combination of Copaxone (glatiramer acetate) and Avonex (IFNβ-1a IM) over 3 years. The ARR for the combination therapy (IFNβ-1a IM + glatiramer) was not statistically superior to the better of the 2 single treatment arms (glatiramer) (p = 0.27). The ARRs were 0.12 for the combination therapy, 0.16 for IFNβ-1a IM, and 0.11 for glatiramer acetate. Glatiramer acetate performed significantly better than IFNβ-1a IM, reducing the risk of exacerbation by 31% (p = 0.027), and IFNβ-1a IM + glatiramer acetate performed significantly better than IFNβ-1a IM, reducing the risk of exacerbation by 25% (p = 0.022). The 3 treatment groups did not show a significant difference in disability progression over 6 months. Combination therapy was superior to either monotherapy in reducing new lesion activity and accumulation of total lesion volume *(Lublin et al 2013)*.
- It is estimated that within a few years of initiating treatment, at least 30 and 15% of patients discontinue MS biological response modifiers due to perceived lack of efficacy or side effects, respectively *(Coyle 2008, Portaccio et al 2008)*. According to several observational studies, switching patients who have failed to adequately respond to initial treatment to another recommended therapy is safe and effective *(Caon et al 2006, Carra et al 2008, Zwibel 2006)*. Patients switching to glatiramer acetate after experiencing an inadequate response to IFNβ-1a therapy had a reduction in relapse rates and disability progression. Likewise, switching to IFNβ-1a therapy after suboptimal efficacy with glatiramer acetate increased the number of relapse-free patients in 1 study *(Carra et al 2008)*. The smallest reduction in the ARR was seen in patients who had switched from one IFNβ-1a preparation to another.
- The GALA study evaluated glatiramer acetate SC 40 mg 3 times weekly compared to placebo in 1404 patients with relapsing MS over 12 months. Results demonstrated that glatiramer acetate 40 mg 3 times weekly, compared to placebo, reduced the ARR and MRI endpoints *(Khan et al 2013)*.
- A Phase 3 dose comparison study evaluated glatiramer acetate 20 mg and 40 mg each given daily in 1155 patients with MS. The primary endpoint, mean ARR, was similar in both groups: ARR = 0.33 (20 mg group) vs ARR = 0.35 (40 mg group). For patients from both groups who completed the entire 1-year treatment period, the mean ARR = 0.27 *(Comi et al 2011)*.
- The efficacy and safety of Plegridy (peginterferon β-1a) in adult patients with MS (n = 1516) were evaluated in ADVANCE, a Phase 3, multicenter, placebo-controlled, RCT. Eligible adult patients had RRMS with a baseline Expanded Disability Status Scale (EDSS) score ≤ 5 and 2 clinically documented relapses in the previous 3 years with at least 1 relapse in the previous 12 months. Patients were randomized to placebo or SC peginterferon β-1a 125 mcg every 2 weeks or every 4 weeks for 48 weeks. Approximately 81% of patients were treatment naïve.
  - At week 48, ARRs were significantly lower in the peginterferon β-1a every 2 week group (ARR = 0.256; p = 0.0007) and peginterferon β-1a every 4 week group (ARR = 0.288; p = 0.0114) compared to placebo (ARR = 0.397).
  - There were also significant differences between the peginterferon β-1a every 2 weeks and every 4 weeks groups compared to placebo in the proportion of patients with relapse at week 48 (p = 0.0003 and p = 0.02, respectively). The proportions of patients with 12 weeks of sustained disability progression at the end of the 48 week study period were significantly lower in the peginterferon β-1a groups (both 6.8%; p = 0.0383 for every 2 weeks group; p = 0.038 for every 4 weeks group) compared to placebo (10.5%).
  - The mean number of new or newly enlarging T2 hyperintense lesions on MRI were significantly reduced in the peginterferon β-1a every 2 weeks group compared to placebo (3.6 lesions vs 10.9 lesions, respectively; p < 0.0001). Significant beneficial effects on the mean number of Gadolinium (Gd)-enhancing lesions were also observed with peginterferon β-1a every 2 weeks compared to placebo (p < 0.0001).
  - During the 48 weeks of treatment, the most commonly reported adverse effects included influenza-like illness and injection site erythema. Discontinuations due to adverse effects were higher in the peginterferon β-1a groups compared to placebo *(Calabresi et al 2014[b])*. NAb to IFN β-1a were identified in < 1% of all groups after 1 year (peginterferon β-1a SC every 2 weeks, 4 patients; peginterferon β-1a SC every 4 weeks, 2 patients; placebo, 2 patients) *(Calabresi et al 2014[b])*. Preliminary data on NAb development to peginterferon β-1a over 2 years showed < 1% for all groups *(White et al 2014)*.
- The ADVANCE study continued into a second year. Patients originally randomized to placebo were re-randomized to peginterferon β-1a (the “placebo-switch group”). Peginterferon β-1a patients were continued on their original assigned therapy. A total of 1332 patients entered the second year of the study. After 96 weeks, the ARR was significantly lower in the peginterferon β-1a SC every 2 weeks group (ARR 0.221; p = 0.0001 vs placebo-switch group; p = 0.0209 vs every 4 week regimen) compared to both the placebo-switch group (ARR 0.351) and the peginterferon β-1a SC every 4 week group (ARR 0.291). The peginterferon β-1a SC every 4 week group (ARR 0.291; p = NS vs placebo-switch group) was

not significantly different from the placebo-switch group (ARR 0.351) after 96 weeks based on the intent-to-treat (ITT) analysis. Peginterferon β-1a SC every 2 weeks was also associated with a lower proportion of patients who had relapse and a lower proportion of patients who had disability progression. Mean number of new or newly enlarging T2-weighted hyperintense MRI lesions over 2 years was numerically lower with the peginterferon β-1a SC every 2 weeks group compared to the placebo-switch group *(Calabresi et al 2014[b], Kieseier et al 2015)*.

- The ATTAIN study was an open-label extension of the ADVANCE study, where patients were followed for an additional 2 years (*Newsome et al 2018*). Of the original ADVANCE patients, 71% continued into the ATTAIN study, and 78% of those patients completed the extension study. The primary objective of the study was to evaluate the long-term safety of peginterferon β-1a SC. During the study, the common adverse events were influenza-like illness (43%), injection site erythema (41%), and headache (29%). The rate of treatment-related serious adverse events was 1%. The adjusted ARR and risk of relapse were reduced significantly with the every 2 weeks compared to the every 4 weeks dosing group (0.188 vs 0.263 and 36% vs 49%, respectively).
- Bioequivalency was demonstrated for Plegridy administered by IM and SC injection in an unpublished, open-label, crossover, single-dose, Phase 1 study of 136 healthy volunteers; this study was the basis for the FDA-approval of the IM route of administration for Plegridy (*Zhao et al 2020*). Injection site reactions were reported less frequently after IM dosing (14.4%) than after SC dosing (32.1%).

ORAL AGENTS

Aubagio (teriflunomide)

- Efficacy and safety of Aubagio (teriflunomide) were evaluated in two Phase 3, double-blind, placebo-controlled, RCTs – the TEMSO trial (*O'Connor et al, 2011*) and the TOWER trial *(Confavreux et al 2014)*. In the TEMSO trial, 1088 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for a total of 108 weeks. Results demonstrated that compared to placebo, teriflunomide at both doses, reduced the ARR.
  - The percentage of patients with confirmed disability progression (CDP) at 12 weeks was significantly lower only in the teriflunomide 14 mg group (20.2%) compared to placebo (27.3%; p = 0.03) *(O'Connor et al 2011)*.
- Teriflunomide has demonstrated beneficial effects on MRI scans in a Phase 2, double-blind, RCT. A total of 179 patients with MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for 36 weeks and were followed every 6 weeks with MRI scans during the treatment period. The teriflunomide groups had significant reductions in the average number of unique active lesions per MRI scan *(O'Connor et al 2006)*.
- In the TOWER trial, 1165 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for at least 48 weeks of therapy. The study ended 48 weeks after the last patient was randomized. Results demonstrated that, compared to placebo, teriflunomide 14 mg significantly reduced the ARR and the risk of sustained accumulation of disability at 12 weeks *(Confavreux et al 2014)*.
- Teriflunomide and Rebif (IFNβ-1a SC) were compared in the 48-week TENERE study evaluating 324 patients with relapsing MS. The primary outcome, time to failure defined as a confirmed relapse or permanent discontinuation for any cause, was comparable for teriflunomide 7 mg and 14 mg and Rebif *(Vermersch et al 2014)*.

Mavenclad (cladribine)

- The 96-week Phase 3 trial, CLARITY, was a double-blind, 3-arm, placebo-controlled, multicenter RCT to evaluate the safety and efficacy of oral cladribine in 1326 patients with RRMS (*Giovannoni et al 2010*, *Giovannoni 2017*).
  - Patients were required to have at least 1 relapse in the previous 12 months. The median patient age was 39 years and the female-to-male ratio was 2:1. The mean duration of MS prior to study enrollment was 8.7 years.
  - Patients were randomized to receive either placebo (n = 437), or a cumulative oral dose of cladribine 3.5 mg/kg (n = 433) or 5.25 mg/kg (n = 456) over the 96-week study period in 2 treatment courses.
  - The primary outcome was ARR:
    - ARRs at 96 weeks were reduced in both cladribine treatment groups vs placebo (0.14, 0.15, and 0.33 in the 3.5 mg/kg, 5.25 mg/kg and placebo groups, respectively; each p < 0.001).
  - A significantly higher percentage of patients remained relapse-free at 96 weeks in both cladribine treatment groups vs placebo; a total of 79.7% and 78.9% of patients in the 3.5 mg/kg and 5.25 mg/kg groups, respectively, were relapse free vs 60.9% in the placebo group (each p < 0.001 vs placebo).
  - Cladribine 3.5 mg/kg group had a lower risk of 3-month CDP vs placebo (hazard ratio [HR], 0.67; 95% CI, 0.48to 0.93; p = 0.02). Lesions on MRI were significantly lower in the cladribine 3.5 mg/kg group vs placebo (p < 0.001 for all comparisons).

Oral Sphingosine-1-phosphate (S1P) receptor modulators

Gilenya (fingolimod)

- Gilenya (fingolimod) has been evaluated in 2 large, RCTs in adults against placebo and against Avonex (IFNβ-1a IM). In FREEDOMS, a 24-month placebo-controlled trial, fingolimod (0.5 and 1.25 mg once daily) was associated with significant reductions in ARR compared to placebo (54 and 60%, respectively; p < 0.001 for both). Moreover, fingolimod was associated with reductions in disability progression and a prolonged time to first relapse compared to placebo *(Kappos et al 2010)*. In the 12-month TRANSFORMS trial, fingolimod 0.5 and 1.25 mg once daily significantly reduced ARR by 52 and 40%, respectively, compared to IFNβ-1a 30 mcg IM once weekly (p < 0.001 for both) *(Cohen et al 2010)*. In a 12-month extension of TRANSFORMS, patients initially randomized to IFNβ-1a IM were switched to either dose of fingolimod for 12 additional months and experienced significant reductions in ARR compared to initial treatment with IFNβ-1a IM. Patients switched from IFNβ-1a IM to fingolimod experienced fewer adverse events compared to treatment with IFNβ-1a IM in the core study (86 vs 91% and 91 vs 94% for the 0.5 and 1.25 mg groups, respectively; p values not reported). Fewer patients continuing fingolimod from the core study reported adverse events in the extension period compared to the core study (72 vs 86% and 71 vs 90% for the 0.5 and 1.25 mg doses, respectively; p values not reported) *(Khatri et al 2011)*. The TRANSFORMS extension study followed patients for up to 4.5 years with results consistent with those observed in the first 12 months of the extension study; however, there was significant attrition bias with very few patients enrolled past 36 months *(Cohen et al 2015)*.
- In the FREEDOMS II study, a 24-month placebo-controlled study, fingolimod (0.5 mg and 1.25 mg) significantly reduced ARR compared to placebo (48 and 50%, respectively; both p < 0.0001) *(Calabresi et al 2014[a])*. Mean percentage brain volume change was lower with both fingolimod doses compared to placebo. Fingolimod did not show a significant effect on time to disability progression at 3 months compared to placebo.
- Fingolimod has also been evaluated in pediatric patients with relapsing MS (*Chitnis et al 2018*). The PARADIGMS trial randomized patients between 10 and 17 years of age to fingolimod 0.5 mg daily (0.25 mg for patients ≤ 40 kg) or IFNβ-1a IM 30 mcg weekly for up to 2 years. Fingolimod significantly reduced ARR compared to IFNβ-1a IM (adjusted rates, 0.12 vs 0.67; relative difference of 82%; p < 0.001). Fingolimod was also associated with a 53% relative reduction in the annualized rate of new or newly enlarged lesions on MRI. However, serious adverse events occurred more frequently with fingolimod than IFNβ-1a IM (16.8% vs 6.5%, respectively).

Mayzent (siponimod)

- The Phase 3 EXPAND trial was a double-blind, parallel-group, placebo-controlled, time-to-event RCT in patients with SPMS who had evidence of disability progression in the previous 2 years (*Kappos et al 2018*). A total of 1651 patients were randomized to treatment with either siponimod 2 mg (n = 1105) or placebo (n = 546). A total of 82% of the siponimod-treated patients and 78% of placebo-treated patients completed the study. The median age of patients was 49.0 years, 95% of patients were white, and 60% were female.
  - For the primary endpoint, 288 (26%) of 1096 patients receiving siponimod and 173 (32%) of 545 patients receiving placebo had a 3-month CDP (HR, 0.79; 95% CI, 0.65 to 0.95; p = 0.013).
  - Key secondary endpoints included time to 3-month confirmed worsening of at least 20% from baseline in timed 25-foot walk (T25FW) and change from baseline in T2 lesion volume on MRI. Siponimod did not show a significant difference in T25FW.
  - Patients treated with siponimod had a 55% relative reduction in ARR (0.071 vs 0.16), compared to placebo (nominal p < 0.01). The absolute reduction in the ARR was 0.089 with siponimod.

Zeposia (ozanimod)

- The efficacy and safety of ozanimod were compared to Avonex (IFNβ-1a IM) in two multicenter, Phase 3, double-blind, double-dummy RCTs in patients with relapsing forms of MS– SUNBEAM and RADIANCE (*Comi et al 2019, Cohen et al 2019)*. In the studies, which were conducted over a minimum of 12 months, patients were randomized 1:1:1 to oral ozanimod 0.5 mg daily, oral ozanimod 1 mg daily, or Avonex (IFNβ-1a) 30 mcg IM once weekly. All patients received an initial 7-day dose escalation of ozanimod or placebo prior to receiving their assigned dose on day 8. Prophylactic administration of acetaminophen or ibuprofen was recommended 1 hour before each IFN or placebo injection and every 6 hours for 24 hours after the injection. Patients in both trials (n = 1346 for SUNBEAM and n = 1320 for RADIANCE) had an EDSS score of ≤ 5, and a history of at least 1 relapse within 12 months prior to screening or 1 relapse within 24 months in addition to at least 1 Gd-enhancing lesion within 12 months prior to screening. The primary endpoint in both trials was the ARR.

- In the SUNBEAM, the ARR was 0.18 (95% CI, 0.14 to 0.24) for ozanimod 1 mg, 0.24 (95% CI, 0.19 to 0.31) for ozanimod 0.5 mg, and 0.35 (95% CI, 0.28 to 0.44) for IFNβ-1a IM. Significant reductions in ARR were observed compared to IFNβ-1a IM with both ozanimod 1 mg (rate ratio, 0.52; 95% CI, 0.41 to 0.66; p < 0.0001) and ozanimod 0.5 mg (rate ratio, 0.69; 95% CI, 0.55 to 0.86; p = 0.0013).
- In the RADIANCE trial, adjusted ARRs were found to be 0.17 (95% CI, 0.14 to 0.21) for ozanimod 1 mg, 0.22 (95% CI, 0.18 to 0.26) for ozanimod 0.5 mg, and 0.28 (95% CI, 0.23 to 0.32) for IFNβ-1a IM. The rate ratios were significant when comparing ozanimod 1 mg (rate ratio, 0.62; 95% CI, 0.51 to 0.77; p < 0.0001) and ozanimod 0.5 mg (rate ratio, 0.79; 95% CI, 0.65 to 0.96; p = 0.0167) to IFNβ-1a IM.
- Clinically significant evidence of bradycardia, second-, or third-degree heart block was not noted after administration of the first dose in either trial.

Oral Fumarates

Tecfidera (dimethyl fumarate)

- Tecfidera (dimethyl fumarate) was evaluated in two Phase 3 studies: DEFINE and CONFIRM *(Fox et al 2012, Gold et al 2012, Xu et al 2015)*. DEFINE was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo in 1237 patients with RRMS over 96 weeks. Results demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, the number of lesions on MRI, and the proportion of patients with disability progression at 12 weeks *(Gold et al 2012)*.
- CONFIRM was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo, with an additional, open-label study arm evaluating glatiramer acetate 20 mg SC daily. Glatiramer acetate was included as a reference comparator, but the study was not designed to test the superiority or non-inferiority of dimethyl fumarate vs glatiramer acetate. There were 1430 patients enrolled, and the trial duration was 96 weeks. Results of CONFIRM were similar to DEFINE, with the exception that there was no significant difference between groups in the likelihood of confirmed disability progression at 12 weeks. The CONFIRM trial demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, and the number of lesions on MRI *(Fox et al 2012)*.

Vumerity (diroximel fumarate)

- The efficacy of diroximel fumarate was established through bioavailability studies in patients with relapsing forms of MS and healthy subjects comparing oral dimethyl fumarate to diroximel fumarate (*Vumerity Prescribing Information 2020*).
- In a Phase 3, open-label, long-term safety study, 696 patients with RRMS (EVOLVE-MS-1) were administered diroximel fumarate 462 mg twice daily for up to 96 weeks (*Palte et al 2019*). Interim results revealed that GI treatment-emergent adverse events occurred in 215 (30.9%) of patients; the vast majority of these events (207 [96%]) were mild or moderate in severity. Gastrointestinal events occurred early in therapy, resolved (88.8%; 191/215), and were of short duration (median 7.5 days) in most patients. Discontinuation of treatment due to a GI treatment-emergent adverse event occurred in < 1% of patients.
- Topline results from the randomized, double-blind, 5-week, Phase 3, EVOLVE-MS-2 study also demonstrated significantly improved GI tolerability with diroximel fumarate vs dimethyl fumarate in 506 patients with RRMS (*Selmaj et al 2019*). Patients were randomized to diroximel fumarate 462 mg twice daily or dimethyl fumarate 240 mg twice daily. The primary endpoint was the number of days patients reported GI symptoms with a symptom intensity score ≥ 2 on the Individual Gastrointestinal Symptom and Impact Scale (IGISIS) rating scale. Results revealed that patients treated with diroximel fumarate self-reported significantly fewer days of key GI symptoms with intensity scores ≥ 2 as compared to dimethyl fumarate (p = 0.0003). The most commonly reported adverse events for both groups were flushing, diarrhea, and nausea.

Bafiertam (monomethyl fumarate)

- The efficacy of monomethyl fumarate, the active moiety of dimethyl fumarate, is based on bioavailability studies in healthy patients comparing oral dimethyl fumarate delayed-release capsules to monomethyl fumarate delayed-release capsules. Analyses compared the blood levels of monomethyl fumarate to establish bioequivalency and support the FDA approval (*Bafiertam Prescribing Information 2020*).

High Efficacy Infusibles and Injectables

Tysabri (natalizumab)

- Tysabri (natalizumab) reduced the risk of experiencing at least 1 new exacerbation at 2 years and reduced the risk of experiencing progression at 2 years *(Polman et al 2006, Pucci et al 2011, Rudick et al 2006)*. The AFFIRM trial compared natalizumab to placebo in patients with MS with less than 6 months of treatment experience with any DMT. Natalizumab reduced the ARR at 1 and 2 years compared to placebo. The cumulative probability of sustained disability progression and lesion burden on MRI were significantly reduced with natalizumab compared to placebo *(Polman et al 2006)*. In the SENTINEL trial, natalizumab was compared to placebo in patients who were receiving IFNβ-1a IM 30 mcg once weekly for at least 1 year. The combination of natalizumab plus IFNβ-1a IM resulted in a significant reduction in ARR at year 1 and 2 and significant reduction in cumulative probability of sustained disability progression at year 2. Lesion burden on MRI was also significantly reduced with the combination therapy. Two cases of PML were reported in the SENTINEL patient population resulting in the early termination of the trial *(Rudick et al 2006)*.

Lemtrada (alemtuzumab)

- The efficacy and safety of alemtuzumab were compared to Rebif (IFNβ-1a SC) in two Phase 3, open-label RCTs in patients with relapsing forms of MS – CARE-MS I and CARE-MS II (*Cohen et al 2012, Coles et al 2012)*. In the 2-year studies, patients were randomized to alemtuzumab infused for 5 consecutive days followed by a 3 consecutive day treatment course 12 months later or to Rebif (IFNβ-1a SC) 44 mcg 3 times weekly after an initial dosage titration. All patients received methylprednisolone 1 g IV for 3 consecutive days at the initiation of treatment and at month 12.
  - The CARE-MS I trial enrolled treatment-naïve patients with MS (n = 581) who were high functioning based on the requirement of a score of 3 or lower on the EDSS.
  - Patients (n = 840) enrolled in the CARE-MS II trial had experienced at least 1 relapse while on IFNβ or glatiramer acetate after at least 6 months of treatment. Patients were required to have an EDSS score of ≤ 5.
  - The co-primary endpoints for both trials were the relapse rate and the time to 6-month sustained accumulation of disability.
  - In the CARE-MS I trial, alemtuzumab reduced the risk of relapse by 55% compared to IFNβ-1a SC ($p < 0.0001$). Relapses were reported in 22% of alemtuzumab-treated patients and 40% of IFNβ-1a SC patients over 2 years. The proportion of patients having sustained accumulation of disability over 6 months was not significantly different between alemtuzumab (8%) vs IFNβ-1a SC (11%) ($p = 0.22$).
  - In the CARE-MS II trial, alemtuzumab significantly reduced the relapse rate and sustained accumulation of disability compared to IFNβ-1a SC. The relapse rate at 2 years was reduced by 49% with alemtuzumab ($p < 0.0001$). The percent of patients with sustained accumulation of disability confirmed over 6 months was 13% with alemtuzumab and 20% with IFNβ-1a SC, representing a 42% risk reduction with alemtuzumab ($p = 0.0084$).
  - Both studies evaluated MRI outcomes, specifically the median percent change in T2 hyperintense lesion volume from baseline. Neither study found a significant difference between the 2 drugs for this measure.
  - During extension studies of CARE-MS I and CARE-MS II, approximately 80% of patients previously treated with alemtuzumab did not require additional treatment during the first year of the extension study *(Garnock-Jones 2014)*.
- A Cochrane review by Zhang et al (2017) that compared the efficacy, tolerability, and safety of alemtuzumab vs IFNβ-1a in the treatment of RRMS identified 3 RCTs in 1694 total patients from the CARE-MS I, CARE-MS II, and CAMMS223 studies. In the alemtuzumab 12 mg/day group, the results showed statistically significant differences in reducing relapses (RR, 0.60, 95% CI, 0.52 to 0.70); preventing disease progression (RR, 0.60, 95% CI, 0.45 to 0.79); and developing new T2-weighted lesions on MRI (RR, 0.75, 95% CI, 0.61 to 0.93) after 24 and 36 months' follow-up, but found no statistically significant difference in the changes of EDSS score (MD = -0.35, 95% CI, -0.73 to 0.03). The most frequently reported adverse effects with alemtuzumab were infusion-associated reactions, infections, and autoimmune events.

Kesimpta (ofatumumab)

- The two Phase 3, double-blind, double-dummy, active-controlled, multicenter, RCTs, the ASCLEPIOS I and II trials, included 1882 patients with relapsing MS who were treated with ofatumumab 20 mg SC every 4 weeks or teriflunomide 14 mg daily for up to 30 months. Approximately 40% of the patients in each group had no prior exposure to DMTs. Ofatumumab significantly reduced the ARR, the primary endpoint, compared with teriflunomide.
  - ASCLEPIOS I: ARR: 0.11 vs 0.22; difference, -0.11; 95% CI, -0.16 to -0.06; $p < 0.001$; RR, 0.49; 95% CI, 0.37 to 0.65; $p < 0.001$.
  - ASCLEPIOS II: ARR: 0.10 vs 0.25; difference, -0.15; 95% CI, -0.20 to -0.09; $p < 0.001$; RR, 0.42; 95% CI, 0.31 to 0.56; $p < 0.001$.

- Pooled data demonstrated that the percentage of patients with confirmed disability worsening at 3 months was 10.9% vs 15.0% for ofatumumab vs teriflunomide, respectively (HR, 0.66; 95% CI, 0.50 to 0.86; p = 0.002). For the confirmed disability worsening at 6 months, the percentage was also lower in the ofatumumab group (8.1% vs 12.0%; HR, 0.68; 95% CI, 0.50 to 0.92; p = 0.01). There was no significant difference between the groups for disability improvement.
- For the MRI endpoints, the ofatumumab group had significantly fewer mean number of Gd-enhancing lesions and mean number of new or enlarging lesions per year on T2-weighted MRI (all p < 0.001). Brain volume loss did not differ significantly between groups in either trial *(Hauser et al 2020[a])*.

Ocrevus (ocrelizumab)

- The Phase 3 clinical development program for ocrelizumab (ORCHESTRA) included 3 studies: OPERA I, OPERA II, and ORATORIO *(Hauser et al 2017, Montalban et al 2017)*.
  - OPERA I and OPERA II were 2 identically-designed, 96-week, Phase 3, active-controlled, double-blind, double-dummy, multicenter, parallel-group, RCTs that evaluated the efficacy and safety of ocrelizumab (600 mg administered as an IV infusion given as 2-300 mg infusions separated by 2 weeks for dose 1 and then as a single 600 mg infusion every 6 months for subsequent doses) compared with Rebif (IFNβ-1a 44 mcg SC 3 times weekly) in 1656 patients with relapsing MS *(Hauser et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*.
    - Across both studies, the majority of patients had not been treated with a DMT in the 2 years before screening (range: 71.4% to 75.3%); of those patients that had received a previous DMT as allowed by the protocol, most received IFN (18.0% to 21.0%) or glatiramer acetate (9.0% to 10.6%).
    - Ocrelizumab achieved statistically significant reductions in the ARR vs Rebif (IFNβ-1a SC) across both trials (primary endpoint).
      - OPERA I (0.16 vs 0.29; 46% lower rate with ocrelizumab; p < 0.001)
      - OPERA II (0.16 vs 0.29; 47% lower rate; p < 0.001)
    - In pre-specified pooled analyses (secondary endpoints), the percentage of patients with disability progression confirmed at 12 weeks was statistically significantly lower with ocrelizumab vs Rebif (9.1% vs 13.6%; HR, 0.60, 95% CI, 0.45 to 0.81; p < 0.001). The results were similar for disability progression confirmed at 24 weeks (6.9% vs 10.5%; HR, 0.60, 95% CI, 0.43 to 0.84; p = 0.003). The percentages of patients with disability improvement confirmed at 12 weeks were 20.7% in the ocrelizumab group vs 15.6% in the Rebif group (33% higher rate of improvement with ocrelizumab; p = 0.02).
    - The mean numbers of Gd-enhancing lesions per T1-weighted MRI scan were statistically significantly reduced with ocrelizumab vs Rebif (secondary endpoint).
      - OPERA I: 0.02 vs 0.29 (rate ratio = 0.06, 95% CI, 0.03 to 0.10; 94% lower number of lesions with ocrelizumab; p < 0.001)
      - OPERA II: 0.02 vs 0.42 (rate ratio = 0.05, 95% CI, 0.03 to 0.09; 95% lower number of lesions; p < 0.001)
    - The most common adverse events were infusion-related reactions and infections.
  - No opportunistic infections, including PML, were reported in any group over the duration of either trial.
    - An imbalance of malignancies was observed with ocrelizumab; across both studies and through 96 weeks, neoplasms occurred in 0.5% (4/825) of ocrelizumab-treated patients vs 0.2% (2/826) of Rebif-treated patients.
    - Among the ocrelizumab-treated patients that developed neoplasms, there were 2 cases of invasive ductal breast carcinoma, 1 case of renal-cell carcinoma, and 1 case of malignant melanoma. Rebif-treated patients with neoplasms included 1 case of mantle-cell lymphoma and 1 case of squamous-cell carcinoma in the chest.
      - Between the clinical cutoff dates of the 2 trials (April 2, 2015 [OPERA I] and May 12, 2015 [OPERA II]) and June 30, 2016, 5 additional cases of neoplasm (2 cases of breast cancer, 2 cases of basal-cell skin carcinoma, and 1 case of malignant melanoma) were observed during the OL extension phase in which all continuing patients received ocrelizumab.
      - As of February 2018, the overall crude incidence rate of malignancies among patients from OPERA I and II who received ocrelizumab in the double-blind period or open-label extension was 0.40 per 100 patient-years of exposure to ocrelizumab. The incidence rate as of the data cutoff of May 2015 after the completion of the DB period was 0.28 for the ocrelizumab group and 0.14 for the IFN β-1a SC group (*Hauser et al 2020[b]*).
      - As of January 2019, the age- and sex-standardized incidence rate of all malignancies in the ocrelizumab all-exposure (all Phase 2 and 3 studies, plus 4 other trials) (0.22 per 100 patient-years; 95% CI, 0.16 to 0.33),

remained stable over time, with confidence intervals overlapping and within epidemiological references from the Surveillance, Epidemiology, and End Results [SEER] Program of the National Cancer Institute, which reports data on cancer incidence in approximately 28% of the general U.S. population (0.31 per 100 patient-years) (*Genentech 2020[a]*)

- Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs in none of 668 females treated with IFN β-1a SC or placebo), the labeling of ocrelizumab recommends that patients follow standard breast cancer screening guidelines (*Genentech 2020[b]*). In an analysis of the all-exposure ocrelizumab population from the trials through January 2019, the incidence rate of female breast cancer using age at event onset methodology was 0.15 (95% CI, 0.08 to 0.27) per 100 patient-years compared to 0.14 per 100 patient-years (95% CI, 0.14 to 0.14) based on SEER (*Genentech 2020[a]*).

- ORATORIO was an event-driven, Phase 3, double-blind, multicenter, placebo-controlled, RCT evaluating the efficacy and safety of ocrelizumab (600 mg administered by IV infusion every 6 months; given as 2-300 mg infusions 2 weeks apart for each dose) compared with placebo in 732 people with PPMS *(Montalban et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*. Double-blind treatment was administered for a minimum of 5 doses (120 weeks) until the occurrence of ~253 events of disability progression in the trial cohort that was confirmed for at least 12 weeks.
  - The majority of patients (~88%) reported no previous use of DMTs within 2 years of trial entry. The proportion of patients with Gd-enhancing lesions was similar (27.5% in the ocrelizumab group vs 24.7% in the placebo group); however, there was an imbalance in the mean number of Gd-enhancing lesions at baseline, with nearly 50% fewer lesions in the placebo group (1.21 vs 0.6) (*Ocrevus FDA Medical and Summary Reviews 2017*).
  - For the primary endpoint, the percentages of patients with 12-week confirmed disability progression were 32.9% with ocrelizumab vs 39.3% with placebo (HR, 0.76, 95% CI, 0.59 to 0.98; p = 0.03).
  - The percentages of patients with 24-week CDP, a secondary endpoint, were 29.6% with ocrelizumab vs 35.7% with placebo (HR, 0.75, 95% CI, 0.58 to 0.98; p = 0.04).
  - Additional secondary endpoints included changes in the T25FW, the total volume of hyperintense brain lesions on T2-weighted MRI, and brain volume loss.
    - The proportion of patients with 20% worsening of the T25FW confirmed at 12 weeks was 49% in ocrelizumab-treated patients compared to 59% in placebo-treated patients (25% risk reduction).
    - From baseline to Week 120, the total volume of hyperintense brain lesions on T2-weighted MRI decreased by 3.37% in ocrelizumab-treated patients and increased by 7.43% in placebo-treated patients (p < 0.001).
    - From Weeks 24 to 120, the percentage of brain volume loss was 0.90% with ocrelizumab vs 1.09% with placebo (p = 0.02).
  - Infusion-related reactions, upper respiratory tract infections, and oral herpes infections occurred more frequently with ocrelizumab vs placebo.
  - Neoplasms occurred in 2.3% (11/486) of patients treated with ocrelizumab vs 0.8% (2/239) of patients who received placebo. Among the ocrelizumab-treated patients that developed neoplasms, there were 4 cases of breast cancer, 3 cases of basal-cell carcinoma, and 1 case in each of the following: endometrial adenocarcinoma, anaplastic large-cell lymphoma (mainly T cells), malignant fibrous histiocytoma, and pancreatic carcinoma. In the placebo group, 1 patient developed cervical adenocarcinoma in situ and 1 patient developed basal-cell carcinoma.
    - Between the clinical cutoff date (July 24, 2015) and June 30, 2016, 2 additional cases of neoplasm (1 case of basal-cell skin carcinoma and 1 case of squamous-cell carcinoma) were detected during the open-label extension phase in which all patients received ocrelizumab.

Symptomatic MS

- Despite the demonstrated efficacy of DMTs, for many patients there is little evidence of their effect on quality of life (QOL) in general or symptom management in particular. Impaired mobility contributes to direct and indirect costs *(Miravelle et al 2011)*.
  - Ampyra (dalfampridine) is the only FDA-approved agent for the symptomatic treatment of impaired mobility in patients with MS. Improvement of walking ability with dalfampridine was demonstrated in two 14-week, double-blind, Phase 3, RCTs of 540 patients of all MS types. Compared to placebo, dalfampridine significantly improved the walking speed by about 25% in approximately one-third of MS patients as measured by the T25FW *(Goodman et al 2009, Jensen et al 2014, Ruck et al 2014)*.

- However, questions have been raised regarding the cost-effectiveness of dalfampridine, and whether treatment leads to a long-term clinically meaningful therapeutic benefit. To address the benefit of long-term therapy with dalfampridine, an open-label, observational study of 52 MS patients with impaired mobility was conducted. Results demonstrated that about 60% of patients were still on treatment after 9 to 12 months. Two weeks after treatment initiation, significant ameliorations could be found for T25FW, maximum walking distance, as well as motoric and cognitive fatigue, which persisted after 9 to 12 months *(Ruck et al 2014)*.

Clinically Isolated Syndrome (CIS)

- IFNs, Copaxone (glatiramer acetate) and Aubagio (teriflunomide) have evidence supporting a significant delay in the time to development of a second exacerbation, compared to placebo, in patients with an isolated demyelinating event.
  - In the PRECISE trial, glatiramer acetate significantly reduced the risk of converting to a CDMS diagnosis by 45% compared to placebo in patients with CIS (p = 0.005). In addition, the time for 25% of patients to convert to CDMS was significantly prolonged with glatiramer acetate compared to placebo (722 vs 336 days; p = 0.0041) *(Comi et al 2009)*. In the 2 year, open-label extension phase of PRECISE, early initiation of glatiramer acetate demonstrated a 41% reduced risk of CDMS compared to delayed glatiramer acetate (HR, 0.59; 95% CI, 0.44 to 0.8; p = 0.0005). Over the 2-year extension, the baseline-adjusted proportions of patients who developed CDMS were 29.4% and 46.5% for the early and late initiation treatment groups (odds ratio [OR]: 0.48; 95% CI, 0.33 to 0.7; p = 0.0002) *(Comi et al 2012)*.
  - A meta-analysis of double-blind, placebo-controlled, RCTs in patients with CIS found a significantly lower risk of CDMS with IFN therapy compared to placebo (p < 0.0001) *(Clerico et al 2008)*. A 10-year, multicenter, RCT with IFNβ-1a IM demonstrated that immediate initiation of therapy in patients with CIS reduced the risk for relapses over 10 years, but it was not associated with improved disability outcomes compared to a control group that also initiated therapy relatively early in the disease *(Kinkel et al 2012)*. Over the 10-year study, the drop-out rate was significant. Similar results were observed with IFNβ-1b (BENEFIT study) over an 8-year observation period. Patients who received treatment early had a lower overall ARR compared to those patients who delayed treatment *(Kappos et al 2007, Edan et al 2014)*. In the first 3 years of BENEFIT, early treatment with IFNβ-1b reduced the risk for progression of disability by 40% compared to delayed treatment (16% vs 25%, respectively; HR, 0.6; 95% CI, 0.39 to 0.92; p = 0.022).
  - A 2018 systematic review and network meta-analysis of RCTs was conducted to assess the potential short- and long-term benefits of treatment with IFN-β or glatiramer acetate in patients with CIS (*Armoiry et al 2018)*. The review identified 5 primary RCTs that assessed the time to CDMS in patients with CIS treated with IFN-β or glatiramer acetate vs placebo. They found that all drugs reduced the time to CDMS when compared with placebo, with a pooled HR of 0.51 (95% CI, 0.44 to 0.61) and low heterogeneity, and there was no evidence that indicated that 1 active treatment was superior to another when compared indirectly. The authors noted that there was insufficient information to rate the risk of selection bias, 4 of the 5 studies were at high risk of performance bias, and 1 study was rated to have a high risk for attrition bias. Four of the trials had open-label extension studies performed over 5 to 10 years, all of which indicated that early DMT therapy (regardless of agent) led to an increase in time to CDMS when compared with placebo (HR, 0.64, 95% CI, 0.55 to 0.74; low heterogeneity). These results should be taken with caution; however, as all of the open-label extension arms were at a high risk for attrition bias and had large losses to follow-up noted.
  - The TOPIC study enrolled 618 patients with CIS and found teriflunomide 7 and 14 mg doses reduced the risk of relapse defining CDMS compared to placebo *(Miller et al 2014)*. Teriflunomide 14 mg reduced the risk of conversion to CDMS by 42.6% compared to placebo (HR, 0.574; 95% CI, 0.379 to 0.869; p = 0.0087) whereas teriflunomide 7 mg reduced the conversion to CDMS by 37.2% compared to placebo (HR, 0.628; 95% CI, 0.416 to 0.949; p = 0.0271).

Progressive MS

- Limited treatment options are available for patients with non-active SPMS and PPMS. Mitoxantrone is FDA-approved for treating SPMS, while ocrelizumab has been specifically approved for the treatment of PPMS (and relapsing forms of MS).
- Mitoxantrone was shown to reduce the clinical relapse rate and disease progression in aggressive RRMS, SPMS, and PRMS *(Hartung et al 2002, Krapf et al 2005)*. For MRI outcome measures, mitoxantrone was not statistically significantly different than placebo at month 12 or 24 for the total number of MRI scans with positive Gd-enhancement or at month 12 for the number of lesions on T2-weighted MRI. However, the baseline MRI lesion number and characteristics were

different among the groups *(Krapf et al 2005)*. In 2010, the Therapeutics and Technology Assessment Subcommittee of the AAN evaluated all published data, including cohort data, for mitoxantrone. An evaluation of efficacy found that mitoxantrone is probably effective in modestly reducing clinical attack rate, MRI activity, and disease progression. A confirmatory trial is necessary before widespread adoption of mitoxantrone for DMT for MS can be made in light of the risks of cardiotoxicity and treatment-related leukemia *(Marriott et al 2010)*.

- The results of studies with the other agents for MS have failed to consistently demonstrate a benefit in progressive forms of MS. In the PROMISE trial, glatiramer acetate was no more effective than placebo in delaying the time to accumulated disability for patients with PPMS *(Wolinsky et al 2007)*. Results from the ASCEND trial, evaluating natalizumab in SPMS, found no significant difference in the rate of confirmed disability progression compared to placebo (*Kapoor et al 2018*).
- Several IFN trials in this population have yielded conflicting results *(Rizvi et al 2004)*. A systematic analysis evaluated 5 clinical trials (N = 3082) of IFNβ compared to placebo in the treatment of SPMS. In 4 trials with the primary outcome of sustained disability progression at 3 or 6 months, IFNβ demonstrated no benefit. The risk ratio for sustained progression with IFNβ was 0.98 (95% CI, 0.82 to 1.16; p = 0.79); however, between-study heterogeneity was high (I^2 = 57%) *(La Mantia et al 2013)*.

Timing of DMT initiation

- The best initial treatment strategy is uncertain, but 2 main concepts include safety focused (IFNs or glatiramer) and efficacy (ie, natalizumab, ocrelizumab, ofatumumab) approaches (*Olek & Mowry 2020b*). Retrospective observational studies have supported the earlier initiation of high efficacy DMT to reduce the risk of disability progression; however, evidence from RCTs is needed to determine the appropriate stage of MS in which to use a high efficacy DMT (*He et al 2020*).
- A 2017 systematic review evaluated the effect of high efficacy immunotherapies (ie, fingolimod, natalizumab, alemtuzumab) at different stages of MS (*Merkel et al 2017*). Twelve publications (9 RCTs + 3 observational studies) were identified as reporting information relevant to the outcomes of early vs delayed initiation of high efficacy DMTs for RRMS. A number of these studies suggested that earlier commencement of high efficacy DMTs resulted in more effective control of relapse activity than their later initiation. The evidence regarding the effect of the timing of high efficacy therapies on disability outcomes was conflicting; additional data are required to answer this question.

Decisions to discontinue DMTs in MS

- Patients with RRMS eventually progress to SPMS. Patients experience worsening disability with or without relapses. Current therapies focus on relapsing forms of MS and are not indicated for non-active SPMS. The decision to discontinue DMTs has not been well studied. The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review evaluating the decision dilemmas surrounding discontinuation of MS therapies in the setting of progressive disease and pregnancy *(Butler et al 2015)*. No studies directly assess continued therapy vs discontinued therapy for MS in comparable populations. Based on a low strength of evidence, long-term all-cause survival is higher for treatment-naïve MS patients who did not delay starting IFNβ-1b by 2 years and used DMT for a longer duration than those who delayed therapy. Very little evidence is available about the benefits and risks of discontinuation of therapy for MS in women who desire pregnancy (*Rae-Grant et al 2018*).

Meta-Analyses

- A 2017 systematic review conducted by the Institute for Clinical and Economic Review (ICER) included ocrelizumab in a comparative efficacy analysis with other DMTs used in the treatment of MS.
  - Network meta-analyses demonstrated that for the treatment of RRMS, alemtuzumab, natalizumab, and ocrelizumab (in that order) were the most effective DMTs for reducing ARRs (~70% reduction vs placebo).
  - Ocrelizumab and alemtuzumab had the greatest reductions in disability progression (53% to 58% reduction vs placebo, respectively), closely followed by natalizumab (44%).
- A systematic review that identified 28 RCTs found that the magnitude of ARR reduction varied between 15 to 36% for all IFNβ products, glatiramer acetate, and teriflunomide; and from 50 to 69% for alemtuzumab, dimethyl fumarate, fingolimod, and natalizumab. The risk of 3-month disability progression was reduced by 19 to 28% with IFNβ products, glatiramer acetate, fingolimod, and teriflunomide; by 38 to 45% for peginterferon IFNβ, dimethyl fumarate, and natalizumab; and by 68% with alemtuzumab *(Fogarty et al 2016)*.
- A total of 39 RCTs evaluating 1 of 15 treatments for MS were analyzed for benefits and acceptability in 25,113 patients with RRMS *(Tramacere et al 2015)*. Drugs included were IFNβ-1b, IFNβ-1a (IM and SC), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, peginterferon IFNβ-1a,

azathioprine, and immunoglobulins. Investigational agents, daclizumab and laquinimod, were also included. The studies had a median duration of 24 months with 60% of studies being placebo-controlled. The network meta-analysis evaluated the recurrence of relapses and disability progression.

- Relapses: alemtuzumab, mitoxantrone, natalizumab, and fingolimod were reported to have greater treatment benefit compared to placebo. Over 12 months (29 studies; N = 17,897):
  - alemtuzumab: RR, 0.40, 95% CI, 0.31 to 0.51; moderate quality evidence
  - mitoxantrone: RR, 0.40, 95% CI, 0.20 to 0.76; low quality evidence
  - natalizumab: RR, 0.56, 95% CI, 0.43 to 0.73; high quality evidence
  - fingolimod: RR, 0.63, 95% CI, 0.53 to 0.74; low quality evidence
  - dimethyl fumarate: RR, 0.78, 95% CI, 0.65 to 0.93; moderate quality evidence
  - daclizumab (no longer on the market): RR, 0.79, 95% CI, 0.61 to 1.02; moderate quality evidence
  - glatiramer acetate: RR, 0.80, 95% CI, 0.68 to 0.93; moderate quality evidence
- Relapses over 24 months vs placebo (26 studies; N = 16,800):
  - alemtuzumab: RR, 0.46, 95% CI, 0.38 to 0.55; moderate quality evidence
  - mitoxantrone: RR, 0.47, 95% CI, 0.27 to 0.81; very low quality evidence
  - natalizumab: RR, 0.56, 95% CI, 0.47 to 0.66; high quality evidence
  - fingolimod: RR, 0.72, 95% CI, 0.64 to 0.81; moderate quality evidence
- Disability worsening over 24 months vs placebo (26 studies; N = 16,800):
  - mitoxantrone: RR, 0.20, 95% CI, 0.05 to 0.84; low quality evidence
  - alemtuzumab: RR, 0.35, 95% CI, 0.26 to 0.48; low quality evidence
  - natalizumab: RR, 0.64, 95% CI, 0.49 to 0.85; moderate quality evidence
- Relapses and disability worsening over 36 months were only tested in 2 studies (CombiRx and CAMMS223). Both studies had a high risk of bias.
- Acceptability: Higher rates of withdrawal due to adverse events compared to placebo over 12 months were reported for teriflunomide (RR, 2.24, 95% CI, 1.5 to 3.34); peginterferon β-1a (RR, 2.8, 95% CI, 1.39 to 5.64); Avonex (RR, 4.36, 95% CI, 1.98 to 9.6); Rebif (RR, 4.83, 95% CI, 2.59 to 9); and fingolimod (RR, 8.26, 95% CI, 3.25 to 20.97).
- Over 24 months, only fingolimod had a significantly higher proportion of participants who withdrew due to any adverse event (RR vs placebo, 1.69, 95% CI, 1.32 to 2.17).
  - mitoxantrone: RR, 9.82, 95% CI, 0.54 to 168.84
  - natalizumab: RR, 1.53, 95% CI, 0.93 to 2.53
  - alemtuzumab: RR, 0.72, 95% CI, 0.32 to 1.61

- Filippini et al (2013) conducted a Cochrane review of 44 RCTs on the relative effectiveness and acceptability of DMTs and immunosuppressants in patients with either RRMS or progressive MS (N = 17,401).
  - On the basis of high quality evidence, natalizumab and Rebif were superior to all other treatments for preventing clinical relapses in the short-term (24 months) in RRMS compared to placebo (OR = 0.32, 95% CI, 0.24 to 0.43; OR = 0.45, 95% CI, 0.28 to 0.71, respectively); they were also more effective than Avonex (OR = 0.28, 95% CI, 0.22 to 0.36; OR = 0.19, 95% CI, 0.06 to 0.6, respectively).
  - Based on moderate quality evidence, natalizumab and Rebif decreased the odds of patients with RRMS having disability progression in the short-term, with an absolute reduction of 14% and 10%, respectively, vs placebo.
  - Natalizumab and Betaseron were significantly more effective (OR = 0.62, 95% CI, 0.49 to 0.78; OR = 0.35, 95% CI, 0.17 to 0.7, respectively) than Avonex in reducing the number of patients with RRMS who had progression at 2 years of follow-up, and confidence in this result was graded as moderate.
  - The lack of convincing efficacy data showed that Avonex, IV immunoglobulins (IVIG), cyclophosphamide, and long-term corticosteroids have an unfavorable benefit-risk balance in RRMS.
- The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a systematic review of 30 RCTs to assess the comparative clinical- and cost-effectiveness of drug therapies for the treatment of RRMS (N = 16,998) (*CADTH 2013).* Results suggested that all active treatments produce statistically significant reductions in ARR compared with no treatment, and that there were clear between-treatment differences.
  - Compared with no treatment, reductions in the ARR were approximately 70% for natalizumab and alemtuzumab, 50% for fingolimod or dimethyl fumarate, and 30% for SC IFNs, glatiramer acetate, or teriflunomide.
  - Among active comparisons, ARRs were lower for Betaseron (0.69, 95% CI, 0.54 to 0.87); Rebif (0.76, 95% CI, 0.59 to 0.98); and fingolimod (0.49, 95% CI, 0.38 to 0.63) compared with Avonex. In addition, ARRs were statistically lower for dimethyl fumarate (0.76, 95% CI, 0.62 to 0.93) compared with glatiramer acetate.

- Compared with placebo, all active treatments exhibited a lower risk of sustained disability progression, but results were only statistically significant for Avonex, Rebif, natalizumab, fingolimod, teriflunomide, and dimethyl fumarate; RR (95% CI) for these agents ranged from 0.59 (95% CI, 0.46 to 0.75) for natalizumab to 0.74 (95% CI, 0.57 to 0.96) for teriflunomide. Between-treatment differences were less apparent.
- Among active comparisons, the risk of sustained disability progression was statistically lower for alemtuzumab (0.59, 95% CI, 0.40 to 0.86) compared with Rebif, and for Betaseron (0.44, 95% CI, 0.2 to 0.80) compared with Avonex.
- Among active comparisons, MRI findings were more favorable for alemtuzumab compared with Rebif, and more favorable for all 3 of fingolimod, Betaseron, and Rebif compared with Avonex. Compared with glatiramer acetate, dimethyl fumarate resulted in a lower mean number of T2 lesions, but the mean number of Gd-enhancing lesions was not statistically different between these 2 treatments.
- The incidence of serious adverse events and treatment discontinuations did not differ significantly between treatments in the majority of trials, except for a higher incidence of treatment discontinuation for Rebif compared to placebo and alemtuzumab.

- Hamidi et al (2018) conducted a systematic review and network meta-analysis of 37 studies including 26 RCTs from a health technology assessment (HTA) report and 11 supplemental RCTs published after the HTA. Eleven agents, including dimethyl fumarate, teriflunomide, IFNs, peginterferon, glatiramer acetate, natalizumab, fingolimod, and alemtuzumab were included and were compared to either placebo or any drug treatment in patients of varying treatment experience levels. Key findings from the network meta-analysis include:
  - Alemtuzumab 12 mg had the highest probability of preventing annual relapses (RR, 0.29, 95% CI, 0.23 to 0.35; high quality evidence).
  - Alemtuzumab 12 mg (RR, 0.40, 95% CI, 0.27 to 0.60; very low quality evidence) was the most effective against progression of disability.
  - Dimethyl fumarate 240 mg and fingolimod 0.5 mg and 1.25 mg were more effective treatments when considering annual relapse and disability progression:
    - Annual relapse:
      - Dimethyl fumarate 240 mg twice daily: RR, 0.5, 95% CI, 0.42 to 0.6; high quality evidence
      - Fingolimod 0.5 mg: RR, 0.46, 95% CI, 0.39 to 0.54; high quality evidence
      - Fingolimod 1.25 mg: RR, 0.45, 95% CI, 0.39 to 0.53; high quality evidence
    - Disability progression:
      - Dimethyl fumarate 240 mg twice daily: RR, 0.65, 95% CI, 0.49 to 0.85; high quality evidence
      - Fingolimod 0.5 mg: RR, 0.71, 95% CI, 0.55 to 0.90; high quality evidence
      - Fingolimod 1.25 mg: RR, 0.71, 95% CI, 0.56 to 0.90; high quality evidence
  - Withdrawal due to adverse events was difficult to assess due to the low quality of available evidence, however, the authors determined that:
    - Fingolimod 1.25 mg (RR, 2.21, 95% CI, 1.42 to 2.5; moderate quality evidence), and Rebif 44 mcg (RR, 2.21, 95% CI, 1.29 to 3.97; low quality evidence) were associated with higher withdrawals due to adverse events when compared with other treatment options.
  - Alemtuzumab 12 mg (mean difference = -0.6; 95% CI, -1.02 to -0.24) was more effective than other therapies in lowering the EDSS.
  - No treatments were found to significantly increase serious adverse events; peginterferon β-1a was associated with more adverse events overall when compared with other medications (RR, 1.66, 95% CI, 1.21 to 2.28).
  - None of the 11 agents studied were associated with a statistically significantly higher risk of mortality when compared to placebo.
- A Bayesian network meta-analysis evaluating DMTs for RRMS ranked the most effective therapies based on SUCRA analysis (*Lucchetta et al 2018*). A total of 33 studies were included in the analysis. For the ARR, alemtuzumab (96% probability), natalizumab (96%), and ocrelizumab (85%) were determined to be the most effective therapies (high-quality evidence).
- A meta-analysis of randomized controlled trials was conducted to evaluate the efficacy and safety of teriflunomide in reducing the frequency of relapses and progression of physical disability in patients with relapsing multiple sclerosis (*Xu et al 2016*). The results showed that teriflunomide (7 and 14 mg) reduced the ARR and teriflunomide 14 mg decreased the disability progression in comparison to placebo (RR, 0.69, 95% CI, 0.55 to 0.87).
- A 2020 network meta-analysis of 34 RCTs compared ofatumumab with other DMTs for RRMS *(Samjoo et al 2020)*. For the outcome of ARR, rate ratios were significantly improved with ofatumumab compared with teriflunomide, IFN β-1a SC

and IM, IFN β-1b, glatiramer acetate, dimethyl fumarate, and fingolimod; no differences were detected in comparisons with cladribine, ocrelizumab, natalizumab, or alemtuzumab. Values for SUCRA indicated alemtuzumab was most likely to be most effective (96%), followed by ofatumumab (91%), natalizumab (88%), and ocrelizumab (85%).

CLINICAL GUIDELINES

- The American Academy of Neurology (AAN) performed a systematic review that included 20 Cochrane reviews and 73 additional articles in order to assess the available evidence on initiation, switching, and stopping DMTs in patients with MS (*Rae-Grant et al 2018)*. The main recommendations were as follows:
  - Starting DMT
    - Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with 2 or more brain lesions that have imaging characteristics consistent with MS (Level B). After discussing the risks and benefits, clinicians should prescribe DMTs to people with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS who decide they want this therapy. (Level B)
    - Clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity. (Level B)
    - Clinicians should monitor the reproductive plans of women with MS and counsel regarding reproductive risks and use of birth control during DMT in women of childbearing potential who have MS. (Level B)
    - Clinicians should counsel men with MS on their reproductive plans regarding treatment implications before initiating treatment with teriflunomide. (Level B)
    - Because of the high frequency of severe adverse events, clinicians should not prescribe mitoxantrone to people with MS unless the potential therapeutic benefits greatly outweigh the risks. (Level B)
    - Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS. (Level B)
    - Clinicians may initiate natalizumab treatment in people with MS with positive anti-JCV antibody indices above 0.9 only when there is a reasonable chance of benefit compared with the low but serious risk of PML. (Level C)
    - Clinicians should offer ocrelizumab to people with PPMS who are likely to benefit from this therapy unless there are risks of treatment that outweigh the benefits. (Level B)
  - Switching DMTs
    - Clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience 1 or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination, over a 1-year period of using a DMT. (Level B)
    - Clinicians should evaluate the degree of disease activity, adherence, adverse event profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use. (Level B)
    - Clinicians should discuss a change to non-injectable or less frequently injected DMTs in people with MS who report intolerable discomfort with the injections or in those who report injection fatigue on injectable DMTs. (Level B)
    - Clinicians should inquire about medication adverse events with people with MS who are taking a DMT and attempt to manage these adverse events, as appropriate (Level B). Clinicians should discuss a medication switch with people with MS for whom these adverse events negatively influence adherence. (Level B)
    - Clinicians should monitor laboratory abnormalities found on requisite laboratory surveillance (as outlined in the medication's package insert) in people with MS who are using a DMT (Level B). Clinicians should discuss switching DMTs or reducing dosage or frequency (where there are data on different doses [eg, interferons, teriflunomide]) when there are persistent laboratory abnormalities. (Level B)
    - Clinicians should counsel people with MS considering natalizumab, fingolimod, ocrelizumab, and dimethyl fumarate about the PML risk associated with these agents (Level B). Clinicians should discuss switching to a DMT with a lower PML risk with people with MS taking natalizumab who are or who become JCV antibody–positive, especially with an index of above 0.9 while on therapy. (Level B)
    - Clinicians should counsel that new DMTs without long-term safety data have an undefined risk of malignancy and infection for people with MS starting or using new DMTs (Level B). If a patient with MS develops a malignancy while using a DMT, clinicians should promptly discuss switching to an alternate DMT, especially for people with MS using fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate (Level B). People with MS with serious infections potentially linked to their DMTs should switch DMTs (does not pertain to PML management in people with MS using DMT). (Level B)

- Clinicians should check for natalizumab antibodies in people with MS who have infusion reactions before subsequent infusions, or in people with MS who experience breakthrough disease activity with natalizumab use (Level B). Clinicians should switch DMTs in people with MS who have persistent natalizumab antibodies. (Level B)
- Physicians must counsel people with MS considering natalizumab discontinuation that there is an increased risk of MS relapse or MRI-detected disease activity within 6 months of discontinuation (Level A). Physicians and people with MS choosing to switch from natalizumab to fingolimod should initiate treatment within 8 to 12 weeks after natalizumab discontinuation (for reasons other than pregnancy or pregnancy planning) to diminish the return of disease activity. (Level B)
- Clinicians should counsel women to stop their DMT before conception for planned pregnancies unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should discontinue DMTs during pregnancy if accidental exposure occurs, unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should not initiate DMTs during pregnancy unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy. (Level B)

  - Stopping DMTs
    - In people with RRMS who are stable on DMT and want to discontinue therapy, clinicians should counsel people regarding the need for ongoing follow-up and periodic reevaluation of the decision to discontinue DMT (Level B). Clinicians should advocate that people with MS who are stable (that is, those with no relapses, no disability progression, and stable imaging) on DMT should continue their current DMT unless the patient and physician decide a trial off therapy is warranted. (Level B)
    - Clinicians should assess the likelihood of future relapse in individuals with SPMS by assessing patient age, disease duration, relapse history, and MRI-detected activity (eg, frequency, severity, time since most recent relapse or Gd-enhanced lesion) (Level B). Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or Gd-enhanced lesions on MRI activity) and have not been ambulatory (EDSS 7 or greater) for at least 2 years. (Level C)
    - Clinicians should review the associated risks of continuing DMTs vs those of stopping DMTs in people with CIS using DMTs who have not been diagnosed with MS. (Level B)

- In September 2019, the MS Coalition published an update to its consensus paper on the principles and current evidence concerning the use of DMTs in MS *(MS Coalition 2019)*. Major recommendations included the following:
  - Initiation of treatment with an FDA-approved DMT is recommended as soon as possible following a diagnosis of relapsing MS, regardless of the person's age. Relapsing MS includes CIS, RRMS, and active SPMS with clinical relapses or inflammatory activity on MRI.
  - Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, ocrelizumab or natalizumab for newly diagnosed individuals with highly active MS.
  - Clinicians should also consider prescribing a high efficacy medication for patients who have breakthrough activity on another DMT, regardless of the number of previously used agents.
  - Treatment with a given DMT should be continued indefinitely unless any of the following occur (in which case an alternative DMT should be considered):
    - Suboptimal treatment response as determined by the individual and his or her treating clinician
    - Intolerable side effects
    - Inadequate adherence to the treatment regimen
    - Availability of a more appropriate treatment option
    - The healthcare provider and patient determine that the benefits no longer outweigh the risks.
  - Movement from one DMT to another should occur only for medically appropriate reasons as determined by the treating clinician and patient.
  - When evidence of additional clinical or MRI activity while on treatment suggests a sub-optimal response, an alternative regimen (eg, different mechanism of action) should be considered to optimize therapeutic benefit.
  - The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed through a shared decision-making process between the patient and his/her treating clinician. Neither an arbitrary restriction of choice nor a mandatory escalation therapy approach is supported by data.
  - Due to significant variability in the MS population, people with MS and their treating clinicians require access to the full range of treatment options for several reasons:
    - MS clinical phenotypes may respond differently to different DMTs.
    - Different mechanisms of action allow for treatment change in the event of a sub-optimal response.

    - Potential contraindications limit options for some individuals.
    - Risk tolerance varies among people with MS and their treating clinicians.
    - Route of delivery, frequency of dosing, and side effects may affect adherence and quality of life.
    - Individual differences related to tolerability and adherence may necessitate access to different medications within the same class.
    - Pregnancy and breastfeeding limit the available options.
  - Individuals' access to treatment should not be limited by their frequency of relapses, level of disability, or personal characteristics such as age, sex, or ethnicity.
  - Absence of relapses while on treatment is a characteristic of treatment effectiveness and should not be considered a justification for discontinuation of treatment.
  - Treatment should not be withheld during determination of coverage by payors as this puts the patient at risk for recurrent disease activity.
- The European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) published updated guidelines in 2018 (*Montalban et al 2018*). The main recommendations reported were the following:
  - The entire spectrum of DMTs should be prescribed only in centers with adequate infrastructure to provide proper monitoring of patients, comprehensive patient assessment, detection of adverse effects, and the capacity to address adverse effects properly if they occur. (Consensus statement)
  - Offer IFN or glatiramer acetate to patients with CIS and abnormal MRI findings with lesions suggesting MS who do not fulfill full criteria for MS. (Strong)
  - Offer early treatment with DMTs in patients with active RRMS, as defined by clinical relapses and/or MRI activity (active lesions: contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually). (Strong)
  - For active RRMS, choosing among the wide range of available drugs from the modestly to highly effective will depend on patient characteristics and comorbidity, disease severity/activity, drug safety profile, and accessibility of the drug. (Consensus statement)
  - Consider treatment with IFN in patients with active SPMS, taking into account, in discussion with the patient, the dubious efficacy, as well as the safety and tolerability profile. (Weak)
  - Consider treatment with mitoxantrone in patients with active SPMS, taking into account the efficacy and specifically the safety and tolerability profile of this agent. (Weak)
  - Consider ocrelizumab for patients with active SPMS. (Weak)
  - Consider ocrelizumab for patients with PPMS. (Weak)
  - Always consult the summary of product characteristics for dosage, special warnings, precautions, contraindications, and monitoring of side effects and potential harms. (Consensus statement)
  - Consider combining MRI with clinical measures when evaluating disease evolution in treated patients. (Weak)
  - When monitoring treatment response in patients treated with DMTs, perform standardized reference brain MRI within 6 months of treatment onset and compare the results with those of further brain MRI, typically performed 12 months after starting treatment. Adjust the timing of both MRIs, taking into account the drug's mechanism and speed of action and disease activity, including clinical and MRI measures. (Consensus statement)
  - When monitoring treatment response in patients treated with DMTs, the measurement of new or unequivocally enlarging T2 lesions is the preferred MRI method, supplemented by Gd-enhancing lesions for monitoring treatment response. Evaluation of these parameters requires high-quality standardized MRI scans and interpretation by highly qualified readers with experience in MS. (Consensus statement)
  - When monitoring treatment safety in patients treated with DMTs, perform a standard reference MRI every year in patients at low risk for PML, and more frequently (3 to 6 months) in patients at high risk for PML (JC virus positivity, natalizumab treatment duration over 18 months) and in patients at high risk for PML who switch drugs at the time the current treatment is discontinued and the new treatment is started. (Consensus statement)
  - Offer a more efficacious drug to patients treated with IFN or glatiramer acetate who show evidence of disease activity, assessed as recommended above. (Strong)
  - When deciding on which drug to switch to, in consultation with the patient, consider patient characteristics and comorbidities, drug safety profile, and disease severity/activity. (Consensus statement)
  - When treatment with a highly efficacious drug is stopped, whether due to inefficacy or safety, consider starting another highly efficacious drug. When starting the new drug, take into account disease activity (clinical and MRI; the greater the disease activity, the greater the urgency to start new treatment), the half-life and biological activity of the

previous drug, and the potential for resumed disease activity or even rebound (particularly with natalizumab). (Consensus statement)
  - Consider continuing a DMT if the patient is stable (clinically and on MRI) and shows no safety or tolerability issues. (Weak)
  - Advise all women of childbearing potential that DMTs are not licensed during pregnancy, except glatiramer acetate 20 mg/mL. (Consensus statement)
  - For women planning a pregnancy, if there is a high risk for disease reactivation, consider using IFN or glatiramer acetate until pregnancy is confirmed. In some very specific (active) cases, continuing this treatment during pregnancy could also be considered. (Weak)
  - For women with persistent high disease activity, it would generally be advised to delay pregnancy. For those who still decide to become pregnant or have an unplanned pregnancy, treatment with natalizumab throughout pregnancy may be considered after full discussion of potential implications; treatment with alemtuzumab could be an alternative for planned pregnancy in very active cases provided that a 4-month interval is strictly observed from the latest infusion until conception. (Weak)
- The 2015 Association of British Neurologists state that all available DMTs are effective in reducing relapse rate and MRI lesion accumulation *(Scolding et al 2015)*. Evidence is less clear on the impact of DMT on long-term disability. Drugs are separated into 2 categories based on relative efficacy. Category 1 – moderate efficacy includes IFNs (including peginterferon), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod. Category 2 – high efficacy includes alemtuzumab and natalizumab – these drugs should be reserved for patients with very active MS.
- According to the 2013 Canadian recommendations for treatment of MS, treatment decisions should be based on the level of concern for the rate and severity of relapses, degree of functional impairment due to relapses, and disability progression. First-line treatment recommendations for RRMS include IFNβ products and glatiramer acetate. Second-line therapies for RRMS include fingolimod and natalizumab *(Freedman et al 2013)*.

SAFETY SUMMARY

Interferons and glatiramer acetate

- Warnings for IFNβ include decreased peripheral blood cell counts including leukopenia, higher rates of depression, suicide and psychotic disorders, injection site reactions, anaphylaxis, congestive heart failure (CHF), potential development of autoimmune disorders (eg, lupus erythematosus), and risk of severe hepatic injury. IFNβ products (Avonex, Rebif, Betaseron, Extavia, and Plegridy) are associated with influenza-like symptoms including musculoskeletal pain, fatigue, and headache. All IFNβ products carry a warning for thrombotic microangiopathy including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Adverse events related to IFNβ therapy appear to be dose-related and transient.
- Glatiramer acetate is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol. Patients treated with glatiramer acetate may experience a transient, self-limited, post-injection reaction of flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat, or urticaria immediately following the injection. Injection site reactions including lipoatrophy and skin necrosis have been reported. Because glatiramer acetate can modify immune response, it may interfere with immune functions. In controlled studies of glatiramer acetate 20 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions, vasodilatation, rash, dyspnea, and chest pain. In a controlled study of glatiramer acetate 40 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions.

Oral agents

- Fingolimod is contraindicated in patients with a variety of cardiac issues and those with a hypersensitivity to the product. Because of a risk for bradyarrhythmia and atrioventricular (AV) blocks, patients should be monitored during Gilenya treatment initiation. In controlled clinical trials, first-degree AV block after the first dose occurred in 4.7% of patients receiving Gilenya and 1.6% of patients on placebo.
  - Posterior Reversible Encephalopathy Syndrome (PRES) has been reported with fingolimod. Patients with pre-existing cardiac disease may poorly tolerate fingolimod and may require additional monitoring. In clinical trials, the most common adverse reactions (incidence ≥ 10% and > placebo) were headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity. If a serious infection develops, consider suspending fingolimod and reassess risks and benefits prior to re-initiation. Elimination of the drug may take up to 2 months thus, monitoring for infections should continue during this time. Do not start fingolimod in patients with an active acute or chronic infection until the infection is resolved. Life-threatening and fatal infections have been

reported in patients taking fingolimod. Establish immunity to varicella zoster virus prior to therapy initiation. Vaccination against human papilloma virus (HPV) should be considered before initiating treatment with fingolimod; HPV infections including papilloma, dysplasia, warts, and HPV-related cancer have been reported in post marketing reports. Safety labeling changes warn of an increased risk of cutaneous malignancies, including melanoma, and lymphoma in patients treated with fingolimod. Clinically significant hepatic injury has occurred in patients treated with fingolimod in the postmarketing setting; hepatic function should be monitored prior to, during, and until 2 months after medication discontinuation. Cases of PML have occurred in the postmarketing setting, primarily in patients who were treated with fingolimod for at least 2 years. At the first sign or symptom suggestive of PML, fingolimod should be withheld and an appropriate diagnostic evaluation performed. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Additionally, severe increases in disability after discontinuation of fingolimod have been described in post marketing reports. Relapses of MS with tumefactive demyelinating lesions on imaging have been observed both during therapy with fingolimod and after discontinuation in post marketing reports. If a severe MS relapse occurs during or after discontinuation of treatment with fingolimod, tumefactive MS should be considered, and imaging evaluation and initiation of appropriate treatment may be necessary.

- Siponimod is contraindicated in patients with a cytochrome P4502C9*3/*3 genotype, presence of Mobitz type II second-degree, third degree AV block or sinus syndrome. It is also contraindicated in patients that have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, Class III/IV heart failure, or decompensated heart failure requiring hospitalization in the past 6 months. Warnings and precautions of siponimod include an increased infection risk, macular edema, increased blood pressure, bradyarrhythmia and AV conduction delays, decline in pulmonary function, and liver injury. Mayzent may result in a transient decrease in heart rate; titration is required for treatment initiation. Consider resting heart rate with concomitant beta-blocker use; obtain cardiologist consultation before concomitant use with other drugs that decrease heart rate. Women of childbearing potential should use effective contraception during and for 10 days after stopping siponimod due to fetal risk. The most common adverse events (incidence > 10%) are headache, hypertension, and transaminase increases.
- Ozanimod is contraindicated in patients that have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, Class III/IV heart failure, or decompensated heart failure requiring hospitalization in the past 6 months. It is also contraindicated in patients with Mobitz type II second- or third-degree atrioventricular block, sick sinus syndrome, or sinoatrial attack unless the patient has a functioning pacemaker. Use is also contraindicated in patients with severe, untreated sleep apnea and those taking a monoamine oxidase inhibitor. Warnings and precautions for ozanimod include an increased infection risk, macular edema, increased blood pressure, bradyarrhythmia and AV conduction delays, decline in pulmonary function, and liver injury. Women of childbearing potential should use effective contraception during and for 3 months after stopping ozanimod due to fetal risk. The most common adverse events (incidence > 10%) are upper respiratory tract infections and hepatic transaminase elevations. Zeposia (ozanimod) does not have a recommendation for first-dose cardiac observation like fingolimod and siponimod.
- Dimethyl fumarate, diroximel fumarate, and monomethyl fumarate are contraindicated in patients with hypersensitivity to the products or any of their excipients. Warnings include anaphylaxis and angioedema, PML, lymphopenia, and clinically significant cases of liver injury. Serious cases of herpes zoster and other opportunistic viral (eg, herpes simplex virus, West Nile virus, cytomegalovirus), fungal (eg, Candida and Aspergillus), and bacterial (eg, Nocardia, Listeria monocytogenes, *Mycobacterium tuberculosis*) infections have been reported in patients treated with dimethyl fumarate, and may occur at any time during treatment with dimethyl fumarate, diroximel fumarate, or monomethyl fumarate. Patients with signs/symptoms of any of these infections should undergo diagnostic evaluation and receive appropriate treatment; treatment with dimethyl fumarate, diroximel fumarate, or monomethyl fumarate may need to be withheld until the infection has resolved. Consider therapy interruption if severe lymphopenia for more than 6 months occurs. Cases of PML have been reported following therapy. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Common adverse events (incidence ≥ 10% and ≥ 2% more than placebo) were flushing, abdominal pain, diarrhea, and nausea. Administration of non-enteric aspirin up to 325 mg given 30 minutes prior to each dose or a temporary dose reduction may reduce flushing. Diroximel fumarate should not be coadministered with dimethyl fumarate.
- Teriflunomide is contraindicated in patients with severe hepatic impairment; pregnancy, those with a history of hypersensitivity to the medication, women of childbearing potential who are not using reliable contraception; and with concurrent use of leflunomide. Labeling includes boxed warnings regarding hepatotoxicity and teratogenicity/embryolethality that occurred in animal reproduction studies at plasma teriflunomide exposures similar to or lower than in humans. Other warnings include bone marrow effects, immunosuppression leading to potential infections, malignancy risk, interstitial lung disease, peripheral neuropathy, severe skin reactions, drug reaction with

eosinophilia and systemic symptoms, and elevated blood pressure. Teriflunomide has a half-life of 4 to 5 months; therefore, use of activated charcoal or cholestyramine in an 11-day regimen upon discontinuation of teriflunomide is recommended to reduce serum levels more rapidly. The most common adverse reactions (≥ 10% and ≥ 2% greater than placebo) are headache, diarrhea, nausea, alopecia, and an increase in alanine aminotransferase (ALT).

- Cladribine is contraindicated in patients with current malignancy, HIV infection, active chronic infection such as hepatitis or tuberculosis, hypersensitivity to cladribine, and in pregnant women. There is a boxed warning for potential malignancy and risk of teratogenicity. The warnings and precautions are lymphopenia, active infection, hematologic toxicity, liver injury, and graft vs host disease with blood transfusion. The most common adverse events (incidence > 20%) are upper respiratory tract infection, headache, and lymphopenia.

High Efficacy Infusibles and Injectables

- Natalizumab has a boxed warning regarding the risk of PML. PML is an opportunistic viral infection of the brain that usually leads to death or severe disability. Due to the risk of PML, natalizumab is only available through the TOUCH® Prescribing Program, which is a restricted distribution program. Natalizumab is contraindicated in patients who have or have had PML and in patients who have had a hypersensitivity reaction. The most common adverse reactions (incidence ≥ 10% in MS) were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea, and rash. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Other warnings with natalizumab include hypersensitivity reactions, increased risk of herpes encephalitis and meningitis, increased risk of infections (including opportunistic infections), thrombocytopenia, and hepatotoxicity.
- Alemtuzumab is contraindicated in patients with human immunodeficiency virus (HIV). The boxed warning for alemtuzumab includes autoimmunity conditions (immune thrombocytopenia, autoimmune hepatitis, and anti-glomerular basement membrane disease), serious and life-threatening infusion reactions, serious and life-threatening stroke within 3 days of administration, and the possibility of an increased risk of malignancies (ie, thyroid cancer, melanoma, and lymphoproliferative disorders/lymphoma).
  - Alemtuzumab is only available through a restricted distribution and REMS program, which requires the member, provider, pharmacy, and infusion facility to be certified.
  - Approximately one-third of patients who received alemtuzumab in clinical trials developed thyroid disorders. The most commonly reported adverse events reported in at least 10% of alemtuzumab-treated patients and more frequently than with IFNβ-1a were rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. Nearly all patients (99.9%) in clinical trials had lymphopenia following a treatment course of alemtuzumab. Alemtuzumab may also increase the risk of acute acalculous cholecystitis; in controlled clinical studies, 0.2% of alemtuzumab-treated MS patients developed acute acalculous cholecystitis, compared to 0% of patients treated with IFNβ-1a. During postmarketing use, additional cases of acute acalculous cholecystitis have been reported in alemtuzumab-treated patients.
  - Other safety concerns within the product labeling include a warning that patients administered alemtuzumab are at risk for serious infections, including those caused by *Listeria monocytogenes,* the potential development of pneumonitis, and PML. Patients that are prescribed alemtuzumab should be counseled to avoid or appropriately heat any foods that may be a source of *Listeria*, such as deli meats and unpasteurized cheeses. Patients should also undergo tuberculosis screening according to local guidelines. With regard to PML, alemtuzumab should be withheld, and appropriate diagnostic evaluations performed, at the initial occurrence of suggestive signs or symptoms.
- The labeling of ocrelizumab does not contain any boxed warnings; however, ocrelizumab is contraindicated in patients with active hepatitis B virus (HBV) infection and in those with a history of life-threatening infusion reactions to ocrelizumab. Additional warnings for ocrelizumab concern infusion reactions, infections, decreased immunoglobulin levels, and an increased risk of malignancies.
  - As of June 30, 2016, the overall incidence rate of first neoplasm among ocrelizumab-treated patients across all 3 pivotal studies and a Phase 2, dose-finding study *(Kappos et al 2011)* was 0.40 per 100 patient-years of exposure to ocrelizumab (6467 patient-years of exposure) vs 0.20 per 100 patient-years of exposure in the pooled comparator groups (2053 patient-years of exposure in groups receiving Rebif or placebo) *(Hauser et al 2017, Ocrevus Formulary Submission Dossier 2017)*.
    - Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs in none of 668 females treated with Rebif or placebo), the labeling of ocrelizumab additionally recommends that patients follow standard breast cancer screening guidelines.

    - No cases of PML were reported in the controlled Phase 2 or 3 studies or in the OLE of these studies. Outside of clinical trials, as of January 31, 2020, there have been 9 confirmed cases of PML in patients treated with ocrelizumab for MS. Of the 9 cases, 8 patients had been switched from natalizumab (n = 7) or fingolimod (n = 1). In 1 additional case, the patient had no prior exposure to DMTs but had contributing factors for PML including advanced age (78 years) and preexisting grade 1 lymphopenia which progressed to grade 2 during treatment (*Genentech 2020[c], Hauser et al 2020[b], Ng et al 2020*).
  - In patients with relapsing MS, the most common adverse reactions with ocrelizumab (incidence ≥ 10% and greater than Rebif) were upper respiratory tract infections and infusion reactions. In patients with PPMS, the most common adverse reactions (incidence ≥ 10% and greater than placebo) were upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.
  - Live or live-attenuated vaccines should not be administered until B-cell count recovery is confirmed (as measured by CD19+ B-cells) in infants born from mothers who were exposed to ocrelizumab during pregnancy.
- Ofatumumab is contraindicated in patients with active hepatitis B virus infection. The prescribing information contains warnings and precautions regarding the risk of infection, injection-related reactions, reduction in immunoglobulins, and fetal risk. The most common adverse events (incidence > 10%) include upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions.
- Mitoxantrone has boxed warnings for the risk of cardiotoxicity, risk of bone marrow suppression, and secondary leukemia. Congestive heart failure, potentially fatal, may occur either during therapy with mitoxantrone or months to years after termination of therapy. The maximum cumulative lifetime dose of mitoxantrone for MS patients should not exceed 140 mg/kg/m^2. Monitoring of cardiac function is required prior to all mitoxantrone doses.

Symptomatic therapy

- Dalfampridine is contraindicated in patients with a history of seizure, moderate or severe renal impairment (CrCl ≤ 50 mL/min), and a history of hypersensitivity to dalfampridine or 4-aminopyridine. Dalfampridine may cause seizures; permanently discontinue this medication in patients who have a seizure while on treatment. Dalfampridine can also cause anaphylaxis; signs and symptoms of anaphylaxis have included respiratory compromise, urticaria, and angioedema of the throat and or tongue. Urinary tract infections (UTIs) were reported more frequently as an adverse reaction in controlled studies in patients receiving dalfampridine 10 mg twice daily (12%) as compared to placebo (8%). The most common adverse events (incidence ≥ 2% and at a rate greater than the placebo rate) for dalfampridine were UTI, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, MS relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain.

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ampyra (dalfampridine)	Tablet	Oral	Twice daily	• May be taken with or without food. Tablets should only be taken whole; do not divide, crush, chew, or dissolve. • In patients with mild renal impairment (CrCl 51 to 80 mL/min), dalfampridine may reach plasma levels associated with a greater risk of seizures, and the potential benefits of dalfampridine should be carefully considered against the risk of seizures in these patients. Dalfampridine is contraindicated in patients with moderate or severe renal impairment (CrCl ≤ 50 mL/min). • There are no adequate and well-controlled studies of dalfampridine in pregnant women; use during pregnancy only if the benefit justifies the potential fetal risk.
Aubagio (teriflunomide)	Tablet	Oral	Once daily	• May be taken with or without food.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• No dosage adjustment is necessary for patients with mild and moderate hepatic impairment; contraindicated in patients with severe hepatic impairment. • Teriflunomide is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for fetal harm. Exclude pregnancy before the start of treatment with teriflunomide in females of reproductive potential and advise females of reproductive potential to use effective contraception during teriflunomide treatment and during an accelerated drug elimination procedure after teriflunomide treatment. Teriflunomide should be stopped and an accelerated drug elimination procedure used if the patient becomes pregnant. • Teriflunomide is detected in human semen; to minimize any possible risk, men not wishing to father a child and their female partners should use effective contraception. Men wishing to father a child should discontinue use of teriflunomide and either undergo an accelerated elimination procedure or wait until verification that the plasma teriflunomide concentration is less than 0.02 mg/L. • Transaminase and bilirubin levels should be obtained within 6 months before initiation; transaminase levels should be monitored for at least 6 months after initiation.
Avonex (interferon β-1a)	Injection; pen, prefilled syringe	IM	Once weekly Titration: To reduce the incidence and severity of flu-like symptoms that may occur during initiation, Avonex may be started at a dose of 7.5 mcg and the dose may be increased by 7.5 mcg each week for the next 3 weeks until the recommended dose of 30 mcg is achieved.	• Following initial administration by a trained healthcare provider, Avonex may be self-administered. • Rotate injection sites to minimize the likelihood of injection site reactions. • Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with Avonex use. • Use caution in patients with hepatic dysfunction.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Bafiertam (monomethyl fumarate)	Capsule (delayed-release)	Oral	Twice daily Titration: 95 mg twice daily for 7 days (initiation), then 190 mg twice daily (maintenance) Temporary dose reductions to 95 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	• May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. • The incidence or severity of flushing may be reduced by administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to monomethyl fumarate; studies did not show that the presence of food had an impact on the incidence of flushing with monomethyl fumarate. • Obtain a complete blood cell count including lymphocyte count, serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiation of therapy.
Betaseron (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	• Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. • Rotate injection sites to minimize the likelihood of injection site reactions. • Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Copaxone (glatiramer acetate) [and Glatopa]	Injection	SC	20 mg once daily **OR** 40 mg 3 times per week at least 48 hours apart Note: The 2 strengths are not interchangeable.	• Following initial administration by a trained healthcare provider, glatiramer acetate may be self-administered. • Areas for SC self-injection include arms, abdomen, hips, and thighs.
Extavia (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	• Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. • Rotate injection sites to minimize the likelihood of injection site reactions. • Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Gilenya (fingolimod)	Capsule	Oral	Once daily Approved for adults and pediatric patients 10 years of age or older. For pediatric patients ≤ 40 kg, a lower dose is recommended.	• May be taken with or without food. First dose monitoring: • Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at end of the observation period are required. • Monitor until resolution if heart rate [HR] < 45 bpm in adults, < 55 bpm in pediatric patients ≥ 12 years of age, or < 60 bpm

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Note: Patients who initiate fingolimod and those who re-initiate treatment after discontinuation for longer than 14 days require first dose monitoring (see right).	in pediatric patients 10 or 11 years of age, new onset second degree or higher AV block, or if the lowest post-dose heart rate is at the end of the observation period. Monitor symptomatic bradycardia with continuous ECG until resolved. Continue overnight if intervention is required; repeat first dose monitoring for second dose. • Observe patients overnight if at higher risk of symptomatic bradycardia, heart block, prolonged QTc interval, or if taking drugs with a known risk of torsades de pointes or drugs that slow heart rate or AV conduction. • Fingolimod exposure is doubled in patients with severe hepatic impairment so patients should be closely monitored. No dose adjustment is necessary in mild-to-moderate hepatic impairment. • The blood level of some fingolimod metabolites is increased (up to 13-fold) in patients with severe renal impairment; blood levels were not assessed in patients with mild or moderate renal impairment. • Fingolimod may cause fetal harm when administered to a pregnant woman. Before initiation of treatment with fingolimod, females of reproductive potential should be counseled on the potential for serious risk to the fetus and the need for effective contraception during treatment and for 2 months after treatment to allow the compound to be eliminated from the body. In females planning to become pregnant, fingolimod should be stopped 2 months before planned conception.
Kesimpta (ofatumumab)	Injection	SC	20 mg at weeks 0, 1, and 2 followed by subsequent dosing of 20 mg once monthly starting at week 4	• Prior to initiation, perform hepatitis B virus screening and tests for quantitative serum immunoglobulins. For patients with low serum immunoglobulins, immunology experts should be consulted.
Lemtrada (alemtuzumab)†	Injection	IV	**2 treatment courses** First course: 12 mg/day on 5 consecutive days Second course: 12 mg/day on 3 consecutive days 12	• Pre-medicate with high-dose corticosteroids prior to Lemtrada infusion for the first 3 days of each treatment course. • Infused over 4 hours for both treatment courses; patients should be observed for

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			months after the first treatment course Subsequent course: 12 mg/day for 3 consecutive days may be administered, as needed, at least 12 months after the last dose of any prior treatment courses.	infusion reactions during and for at least 2 hours after each Lemtrada infusion. Vital signs should be monitored before the infusion and periodically during the infusion. • Administer antiviral agents for herpetic prophylaxis starting on the first day of alemtuzumab dosing and continuing for a minimum of 2 months after completion of Lemtrada dosing or until CD4+ lymphocyte count is > 200 cells/microliter, whichever occurs later. • Patients should complete any necessary immunizations at least 6 weeks prior to treatment with alemtuzumab. Important monitoring: • Complete blood count with differential, serum creatinine, and urinalysis (prior to treatment initiation and at monthly intervals thereafter); a test of thyroid function, such as thyroid stimulating hormone level (prior to treatment initiation and every 3 months thereafter); serum transaminases and total bilirubin (prior to treatment initiation and periodically thereafter) • Measure the urine protein to creatinine ratio prior to treatment initiation • Conduct baseline and yearly skin exams to monitor for melanoma.
Mavenclad (cladribine)	Tablet	Oral	Cumulative dosage of 3.5 mg/kg divided into 2 yearly treatment courses of 1.75 mg/kg per treatment course. Each treatment course is divided into 2 treatment cycles: • First course/first cycle: start anytime • First course/second cycle: administer 23 to 27 days after the last dose of first course/first cycle. • Second course/first cycle: administer at least 43 weeks after the last dose of first course/second cycle.	• The use of Mavenclad in patients weighing less than 40 kg has not been investigated. • Mavenclad is contraindicated in pregnant women and in female/males of reproductive potential that do not plan to use effective contraception. • Follow standard cancer screening guidelines because of the risk of malignancies. • Administer all immunizations according to guidelines prior to treatment initiation. • Obtain a complete blood count with differential including lymphocyte count. Lymphocytes must be within normal limits before treatment initiation and at least 800 cells/microliter before starting the second treatment course.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			• Second course/second cycle: administer 23 to 27 days after the last dose of second course/first cycle.	
Mayzent (siponimod)	Tablet	Oral	Once daily Initiate treatment with a 5-day titration; a starter pack should be used for patients who will be titrated to the maintenance dosage starting on Day 6 (refer to prescribing information for titration regimen).	• Mayzent can cause fetal harm when administered to pregnant women. • Dosage should be titrated based on patient's CYP2C9 genotype. • Patients with sinus bradycardia (HR < 55 bpm), first- or second-degree AV block, or a history of myocardial infarction or heart failure should undergo first dose monitoring for bradycardia.
mitoxantrone	Injection	IV	Every 3 months For MS-related indications: 12 mg/m^2 given as a short IV infusion over 5 to 15 minutes Note: Left ventricular ejection fraction (LVEF) should be evaluated prior to administration of the initial dose of mitoxantrone injection (concentrate) and all subsequent doses. In addition, LVEF evaluations are recommended if signs or symptoms of CHF develop at any time during treatment with mitoxantrone. .	• Mitoxantrone injection (concentrate) should not be administered to MS patients with an LVEF < 50%, with a clinically significant reduction in LVEF, or to those who have received a cumulative lifetime dose of ≥ 140 mg/m^2. • Mitoxantrone generally should not be administered to MS patients with neutrophil counts < 1500 cells/mm^3. • Mitoxantrone therapy in MS patients with abnormal liver function tests is not recommended because mitoxantrone clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments. • Mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant. • Complete blood counts, including platelets, should be monitored prior to each course of mitoxantrone and in the event that signs or symptoms of infection develop. • Liver function tests should be monitored prior to each course of therapy
Ocrevus (ocrelizumab)	Injection	IV	Every 6 months (24 weeks) Titration: Initial dose: 300 mg IV, followed 2 weeks later by a second 300 mg IV infusion. Subsequent doses: 600 mg IV infusion every 6 months	• Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (eg, diphenhydramine) prior to each infusion. An antipyretic (eg, acetaminophen) may also be considered. • Observe patients for at least 1 hour after the completion of the infusion. Dose modifications in response to infusion

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				reactions depend on the severity. See package insert for more details. • Administer all necessary immunizations according to immunization guidelines at least 2 (non-live vaccines) to 4 (live or live-attenuated vaccines) weeks prior to initiation of ocrelizumab. • Women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab. • Hepatitis B virus screening is required before the first dose. • Prior to initiation, quantitative serum immunoglobulin levels should be performed. For patients with low serum immunoglobulins, immunology experts should be consulted.
Plegridy (peginterferon β-1a)	Injection; pen, prefilled syringe for SC use; prefilled syringe for IM use	SC, IM	Every 14 days Titration: Start with 63 mcg on day 1, 94 mcg on day 15, and 125 mcg (full dose) on day 29	• Following initial administration by a trained healthcare provider, Plegridy may be self-administered. • Patients should be advised to rotate injection sites. The usual sites for SC administration are the abdomen, back of the upper arm, and thigh; IM injections should be administered in the thigh. • Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms. • Monitor for adverse reactions due to increased drug exposure in patients with severe renal impairment.
Rebif (interferon β-1a); Rebif Rebidose	Injection	SC	Three times per week at least 48 hours apart Titration: Generally, the starting dose should be 20% of the prescribed dose 3 times per week, and increased over a 4-week period to the targeted recommended dose of either 22 mcg or 44 mcg injected SC 3 times per week	• Following initial administration by a trained healthcare provider, Rebif may be self-administered. • Patients should be advised to rotate the site of injection with each dose to minimize the likelihood of severe injection site reactions or necrosis. • Decreased peripheral blood counts or elevated liver function tests may necessitate dose reduction or discontinuation of Rebif administration until toxicity is resolved. • Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms associated with Rebif use on treatment days.
Tecfidera (dimethyl fumarate)	Capsule (delayed-release)	Oral	Twice daily Titration:	• May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			120 mg twice daily for 7 days (initiation), then 240 mg twice daily (maintenance) Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	• The incidence of flushing may be reduced by administration of dimethyl fumarate with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to dimethyl fumarate dosing may reduce the incidence or severity of flushing. • Obtain a complete blood cell count including lymphocyte count, serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiation of therapy.
Tysabri (natalizumab)†	Injection	IV	Once a month (every 4 weeks) Both MS and Crohn's disease indications are dosed the same: 300 mg infused over 1 hour and given every 4 weeks. Tysabri should not be administered as an IV push or bolus injection.	• Patients should be observed during the infusion and for 1 hour after the infusion is complete.
Vumerity (diroximel fumarate)	Capsule (delayed-release)	Oral	Twice daily Titration: 231 mg twice daily for 7 days (initiation), then 462 mg twice daily (maintenance) Temporary dose reductions to 231 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	• Must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. • Avoid administration with a high-fat, high-calorie meal/snack. Avoid co-administration with alcohol. • The incidence or severity of flushing may be reduced by administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to diroximel fumarate. • Obtain a complete blood cell count including lymphocyte count, serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiation of therapy.
Zeposia (ozanimod)	Capsule	Oral	Once daily Titration: 0.23 mg once daily on days 1 to 4, then 0.46 mg once daily on days 5 to 7, then 0.92 mg once daily on day 8 and thereafter.	• May be taken with or without food. Capsules should be swallowed whole. • Obtain a complete blood count (including lymphocyte count), transaminase and bilirubin levels, electrocardiogram, and ophthalmic assessment before initiation of therapy. • If a dose is missed during the first 2 weeks of treatment, treatment should be restarted using the titration regimen; if a dose is missed after 2 weeks of

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				treatment, continue treatment as planned. • Use in patients with hepatic impairment is not recommended.

*See the current prescribing information for full details
†Currently available through a restricted distribution program as part of a REMS requirement.

CONCLUSION

- DMTs for MS have shown benefits in patients with relapsing MS such as a decreased relapse rate and a slower accumulation of brain lesions on MRI. Therefore, it is recommended that all patients with a diagnosis of definite relapsing MS begin DMTs *(MS Coalition 2019)*.
- IFNβ products have been shown to decrease MRI lesion activity, prevent relapses, and delay disability progression. In general, patients treated with IFNβ or glatiramer acetate can expect a 30% reduction in ARR during a 2-year period *(MS Coalition 2019)*. Head-to-head clinical trials have found IFNβ and glatiramer acetate to be comparable in terms of efficacy on relapse rate. Several studies have demonstrated an improved tolerability at the cost of a decreased therapeutic response with low dose IM IFNβ-1a compared to higher dose SC IFNβ-1a *(Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*.
  - Influenza-type symptoms, injection site reactions, headache, nausea, and musculoskeletal pain are the most frequently reported adverse events with IFNβ products. With IFNβ, use caution in patients with depression or other mood disorders.
  - The most frequently reported adverse events with glatiramer acetate include a transient, self-limiting, post-injection systemic reaction immediately following drug administration consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria. Glatiramer acetate does not have any known drug interactions and is not associated with an increased risk of hepatotoxicity or depression.
- Despite advancements in treatment, many patients fail initial DMTs with glatiramer acetate or IFNβ, primarily due to intolerable adverse effects or inadequate efficacy *(Coyle 2008, Portaccio et al 2008)*. Clinical trials have shown that patients switching from IFNβ to glatiramer acetate therapy and vice versa, due to poor response, may achieve a significant reduction in relapse rates and a delay in disease and disability progression *(Coyle 2008, Caon et al 2006, Zwibel 2006)*. The guidelines suggest that all first-line MS DMTs should be made accessible, and the choice of initial treatment should be based on patient-specific factors *(MS Coalition 2019, Scolding et al 2015, Montalban et al 2018, Rae-Grant et al 2018)*. The premature discontinuation rate is high among patients with MS; therefore, factors that will maximize adherence should be considered when initiating therapy. Failure with 1 agent does not necessarily predict failure with another. Therefore, patients experiencing an inadequate response or drug-induced adverse event should be switched to a different DMT *(Coyle 2008, Portaccio et al 2008, Rae-Grant et al 2018)*.
- There are now 8 available oral agents. It is expected that the availability of oral agents may increase convenience and improve patient adherence *(Sanvito et al 2011)*. The available oral drugs each have different mechanisms of action and/or tolerability profiles. Cases of PML have been reported in patients taking fingolimod and dimethyl fumarate.
  - Gilenya (fingolimod) is a S1P receptor modulator. In a trial comparing fingolimod to placebo, fingolimod-treated patients had a decreased ARR, improved MRI outcomes, and a lower likelihood of disability progression *(Kappos et al 2010)*. In a trial comparing fingolimod to IFNβ-1a IM (Avonex), fingolimod-treated patients had a decreased ARR and improved MRI outcomes, but disability progression was similar in the 2 groups *(Cohen et al 2010)*. The adverse event profile for fingolimod includes cardiovascular risks including bradycardia. First dose administration of fingolimod requires at least 6 hours of observation with hourly monitoring of heart rate and blood pressure, and patients should have an ECG before dosing and at the end of the observation period.
    - Fingolimod is also FDA-approved for MS in the pediatric population. In a trial evaluating patients between 10 and 17 years of age, fingolimod significantly reduced ARR and the rate of new or newly enlarged lesions compared to IFNβ-1a (*Chitnis et al 2018*).
  - Mayzent (siponimod) is a S1P receptor modulator, similar to fingolimod. In a trial comparing Mayzent to placebo, Mayzent significantly reduced the risk of 3-month CDP, delayed the risk of 6-month CDP, and reduced the ARR (*Kappos et al 2018*). First dose cardiac monitoring is recommended for patients with a heart rate < 55 bpm or a history of cardiac disease. Siponimod shares many of the same warnings as fingolimod.

- Zeposia (ozanimod), the third S1P receptor modulator, has to significantly decrease ARR compared to IFNβ-1a; however, unlike other drugs in this class, it does not require first dose cardiac monitoring (*Comi et al 2019, Cohen et al 2019*).
- Tecfidera (dimethyl fumarate) has efficacy similar to that of fingolimod; its benefit-risk profile makes it a reasonable initial or later stage DMT option for most patients with RRMS *(CADTH 2013, Wingerchuk et al 2014)*. Gastrointestinal intolerance and flushing are common side effects that may wane with time; slow titration to maintenance doses, taking the medication with food, and premedication with aspirin may reduce their severity.
- Vumerity (diroximel fumarate) is an oral fumarate that is rapidly converted to monomethyl fumarate, which is also the active metabolite of Tecfidera (dimethyl fumarate). Diroximel fumarate may offer improved GI tolerability as compared to dimethyl fumarate (*Naismith et al 2019, Selmaj et al 2019).*
- Bafiertam (monomethyl fumarate) was approved by the FDA in April 2020 and is considered to be a "bioequivalent alternative" to dimethyl fumarate (*Bafiertam prescribing information 2020*).
- Aubagio (teriflunomide) inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. Although its exact mechanism of action is unknown, it may involve a reduction in the number of activated lymphocytes in the CNS. Patients treated with teriflunomide in a clinical trial experienced a reduction in the ARR and improved MRI outcomes compared to placebo. Patients in the higher dose group (14 mg) also had a lower likelihood of disability progression, but this difference was not statistically significant in the lower dose group (7 mg) as compared to placebo *(O'Connor et al 2011)*. Teriflunomide has boxed warnings for the possibility of severe liver injury and teratogenicity. The most common adverse reactions include increases in liver enzymes, alopecia, diarrhea, influenza, nausea, and paresthesia.
- Mavenclad (cladribine) is a purine antimetabolite indicated for the treatment of relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease. In a trial comparing Mavenclad to placebo, Mavenclad had reduced ARRs and disability progression vs placebo (*Giovannoni et al 2010*). Mavenclad carries a boxed warning for risk of malignancies and teratogenicity. Lymphopenia is the most common adverse effect.

- Tysabri (natalizumab) is a recombinant monoclonal antibody indicated for the treatment of relapsing forms of MS and is also approved for use in the treatment of moderately to severely active CD in patients with an inadequate response to or who are unable to tolerate conventional CD therapies and TNF inhibitors.
  - In a 2011 systematic review of trials evaluating natalizumab for RRMS, pooled efficacy data from 2 RCTs (AFFIRM and SENTINEL) showed that natalizumab significantly reduced the risk for having a relapse during 2 years of treatment. In addition, natalizumab significantly reduced the risk for experiencing 12-week CDP at 2 years *(Pucci et al 2011)*. Natalizumab has been associated with an increased risk of PML; however, the overall incidence of PML has remained low (0.4%). Natalizumab can only be obtained through a restricted distribution program.
- Kesimpta (ofatumumab) is the first self-administered CD20-directed cytolytic antibody indicated for relapsing forms of MS. Ofatumumab has demonstrated superiority to teriflunomide in patients with relapsing forms of MS for the outcome of ARR *(Hauser et al 2020[a])*. Ofatumumab is self-administered monthly by SC injection after an initial loading regimen. Key warnings include the risk for infections, including PML and HBV reactivation. Injection-related reactions, possible reduction in immunoglobulins, and fetal risk (B cell depletion in infants born to mothers treated with ofatumumab during pregnancy) are other warnings. The most common AEs (incidence > 10%) were upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions.
- Ocrevus (ocrelizumab) is a recombinant monoclonal antibody designed to selectively target CD20-positive B cells. As a humanized form of Rituxan (rituximab), ocrelizumab is expected to be less immunogenic with repeated infusions and may have a more favorable benefit-to-risk profile than Rituxan *(Sorensen et al 2016)*.
  - Ocrevus provides another DMT option to the growing armamentarium of highly effective agents indicated for the treatment of relapsing MS. Ocrelizumab is also indicated for the treatment of PPMS, making it the first DMT with substantial evidence supporting its use in this form of MS. Although the pivotal studies of ocrelizumab were of sufficient length to assess efficacy, more long-term safety data are needed to evaluate the effects of ocrelizumab on emergent neoplasms and the risk of PML.
- Lemtrada (alemtuzumab) is a highly efficacious DMT that has demonstrated superiority in reducing relapses when compared to Rebif in both treatment-naïve and treatment-experienced patients. The dosing schedule of 2 annual treatment courses is counterbalanced by the need for regular monitoring of the increased risk for autoimmunity. Lemtrada is best reserved for patients who have failed at least 2 other DMTs and are not candidates for natalizumab (*Garnock-Jones 2014*).

- Mitoxantrone is a synthetic intercalating chemotherapeutic agent. While it is approved for the treatment of RRMS, SPMS, and PRMS, cumulative dose-related cardiac toxicity and the risk for secondary leukemia markedly limit its use. Mitoxantrone is reserved for use in patients with aggressive disease.
- While DMTs do not sufficiently address quality of life in MS patients, dalfampridine can be used to complement treatment with DMTs. Although a 25% improvement in T25FW may appear marginal, it has been established that improvements in T25FW speed of ≥ 20% are meaningful to people with MS. Improved walking could potentially contain some of the direct and indirect costs (eg, reduced productivity, disability, unemployment, costs of assistive devices and caregivers) associated with MS.
- With an increasing number of DMTs currently on the market and no specific MS algorithm in place to guide treatment decisions, the selection of an agent is generally based on considerations of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences.
  - Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, ocrelizumab or natalizumab for newly-diagnosed individuals with highly active MS (*MS Coalition 2019*).
  - Clinicians should also consider prescribing a high efficacy medication for patients who have breakthrough activity on another DMT, regardless of the number of previously used agents (*MS Coalition 2019*).

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Prior Authorization Guideline

Guideline Name Hereditary Angioedema Agents

Formulary OptumRx SP

Formulary Note

Guideline Note:

Effective Date:	3/1/2021
P&T Approval Date:	2/17/2009
P&T Revision Date:	09/18/2019 ; 03/18/2020 ; 07/15/2020 ; 12/16/2020 ; 2/18/2021

1 . Indications

Drug Name: Berinert (C1 esterase inhibitor [Human])
Acute treatment of Hereditary Angioedema (HAE) Indicated for the treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult and adolescent patients. The safety and efficacy of Berinert for prophylactic therapy have not been established.
Drug Name: Cinryze (C1 esterase inhibitor [Human])
Prophylaxis of Hereditary Angioedema (HAE) Indicated for routine prophylaxis against angioedema attacks in adults, adolescents and pediatric patients (6 years old and above) with HAE.

Off Label Uses: Acute treatment of Hereditary Angioedema (HAE) Following treatment with nanofiltered C1 inhibitor concentrate (Cinryze) for an acute attack, the median time to response was 30 minutes in 82 patients with HAE. [3]
Drug Name: Firazyr (icatibant)
Acute treatment of Hereditary Angioedema (HAE) Indicated for the treatment of acute attacks of HAE in adults 18 years of age and older.
Drug Name: Haegarda (C1 esterase inhibitor [Human])
Prophylaxis of Hereditary Angioedema (HAE) Indicated for routine prophylaxis to prevent HAE attacks in patients 6 years of age and older.
Drug Name: Kalbitor (ecallantide)
Acute treatment of Hereditary Angioedema (HAE) Indicated for treatment of acute attacks of HAE in patients 12 years of age and older.
Drug Name: Orladeyo (berotralstat)
Prophylaxis of Hereditary Angioedema (HAE) Indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older. Limitations of Use: Orladeyo should not be used for treatment of acute HAE attacks.
Drug Name: Ruconest (C1 esterase inhibitor [Recombinant])
Acute treatment of Hereditary Angioedema (HAE) Indicated for the treatment of acute attacks in adult and adolescent patients with HAE. Limitation of Use: Effectiveness was not established in HAE patients with laryngeal attacks.
Drug Name: Takhzyro (lanadelumab-flyo)
Prophylaxis of Hereditary Angioedema (HAE) Indicated for prophylaxis to prevent attacks of HAE in patients 12 years and older.

2 . Criteria

Product Name: Cinryze, Haegarda, Orladeyo or Takhzyro	
Diagnosis	Prophylaxis of HAE attacks
Approval Length	12 month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of hereditary angioedema (HAE) [A]

AND

2 - Diagnosis has been confirmed by C1 inhibitor (C1-INh) deficiency or dysfunction (Type I or II HAE) as documented by ONE of the following:

- C1-INH antigenic level below the lower limit of normal
- C1-INH functional level below the lower limit of normal

AND

3 - For prophylaxis against HAE attacks [3]

AND

4 - Prescribed by or in consultation with one of the following: [B]

- Immunologist
- Allergist

Product Name: Cinryze [off-label], Brand Firazyr, Generic icatibant, or Ruconest	
Diagnosis	Treatment of acute HAE attacks
Approval Length	12 month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of hereditary angioedema (HAE) [3, A]

AND

2 - Diagnosis has been confirmed by C1 inhibitor (C1-INh) deficiency or dysfunction (Type I or II HAE) as documented by one of the following:

- C1-INH antigenic level below the lower limit of normal
- C1-INH functional level below the lower limit of normal

AND

3 - For the treatment of acute HAE attacks [3, C]

AND

4 - Not used in combination with other approved treatments for acute HAE attacks

AND

5 - Prescribed by or in consultation with one of the following: [B]

- Immunologist
- Allergist

Product Name: Kalbitor	
Diagnosis	Treatment of acute HAE attacks
Approval Length	12 month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of hereditary angioedema (HAE) [A]

AND

2 - Diagnosis has been confirmed by C1 inhibitor (C1-INh) deficiency or dysfunction (Type I or II HAE) as documented by one of the following:

- C1-INH antigenic level below the lower limit of normal
- C1-INH functional level below the lower limit of normal

AND

3 - For the treatment of acute HAE attacks

AND

4 - Patient is greater than or equal to 12 years of age [D]

AND

5 - Not used in combination with other approved treatments for acute HAE attacks

AND

6 - Prescribed by or in consultation with one of the following: [B]

- Immunologist
- Allergist

Product Name: Berinert	
Diagnosis	Treatment of acute HAE attacks
Approval Length	12 month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of hereditary angioedema (HAE) [3, A]

AND

2 - Diagnosis has been confirmed by C1 inhibitor (C1-INh) deficiency or dysfunction (Type I or II HAE) as documented by one of the following:

- C1-INH antigenic level below the lower limit of normal
- C1-INH functional level below the lower limit of normal

AND

3 - For the treatment of acute HAE attacks [3, C]

AND

4 - Not used in combination with other approved treatments for acute HAE attacks

AND

5 - One of the following:

5.1 Trial and failure, contraindication, or intolerance to Ruconest

OR

5.2 One of the following:

- Patient is 12 years of age or younger
- Documentation that patient has history of laryngeal attacks

AND

6 - Prescribed by or in consultation with one of the following: [B]

- Immunologist
- Allergist

3 . Endnotes

A. HAE is a rare genetic disorder caused by a deficiency of C1-inhibitor and is inherited in an autosomal dominant manner. This condition is characterized by recurrent episodes of angioedema, without urticaria or pruritus, which most often affect the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts. Diagnosis of HAE requires a blood test to confirm low or abnormal levels of C1-inhibitor. [10]

B. Includes immunologist, allergist and rheumatologist specialties to ensure the requirement for proper diagnosing and assessing the severity of the symptoms. In the pivotal Cinryze trial, criteria for participation of long term prophylaxis included patients 9 years and older with documented HAE (based on: a low C4 level plus low C1 inhibitor antigenic level/or low C1 inhibitor functional level OR a known HAE causing mutation) AND a history of at least two HAE attack per month. [1, 8] Berinert is approved for the treatment of acute attacks in patients who are 13 years and older. In the pivotal Berinert trial patients had laboratory-confirmed C1-inhibitor deficiency (type I or II HAE). [9]

C. Following treatment with nanofiltered C1 inhibitor concentrate (Cinryze) for an acute attack, the median time to response was 30 minutes in 82 patients with hereditary angioedema (median number of attacks per patient, 3; range, 1 to 57 attacks) in an open-label extension trial (median follow-up of 11 months). Additionally, 93% of attacks responded within 4 hr after C1 inhibitor concentrate treatment. [3]

D. Kalbitor carries a black box warning that states the following: "Anaphylaxis has been reported after administration of Kalbitor. Because of the risk of anaphylaxis, Kalbitor

should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema (HAE). Healthcare professionals should be aware of the similarity of symptoms between hypersensitivity reactions and hereditary angioedema and patients should be monitored closely. Do not administer Kalbitor to patients with known clinical hypersensitivity to Kalbitor." In 255 HAE patients treated with intravenous or subcutaneous Kalbitor in clinical studies, 10 patients (3.9%) experienced anaphylaxis. For the subgroup of 187 patients treated with subcutaneous Kalbitor, 5 patients (2.7%) experienced anaphylaxis. Symptoms associated with these reactions have included chest discomfort, flushing, pharyngeal edema, pruritus, rhinorrhea, sneezing, nasal congestion, throat irritation, urticaria, wheezing, and hypotension. These reactions occurred within the first hour after dosing. Other adverse reactions indicative of hypersensitivity reactions included the following: pruritus (5.1%), rash (3.1%), and urticaria (2.0%). Patients should be observed for an appropriate period of time after administration of Kalbitor, taking into account the time to onset of anaphylaxis seen in clinical trials. In the Kalbitor HAE program, patients developed antibodies to ecallantide. Rates of seroconversion increased with exposure to ecallantide over time. Overall, 7.4% of patients seroconverted to anti-ecallantide antibodies. Neutralizing antibodies to ecallantide were determined in vitro to be present in 4.7% of patients. Anti-ecallantide and anti-Po pastoris IgE antibodies were also detected. While the long-term effects of antibodies to Kalbitor are not known, patients who seroconvert may be at a higher risk of a hypersensitivity reaction. The manufacturer developed a Risk Evaluation and Mitigation Strategy (REMS) program consisting of a Medication Guide and Communication Plan to notify healthcare professionals of the risk of anaphylaxis and the need to distinguish signs and symptoms of anaphylaxis and HAE attack as they may overlap. The presence of the black box warning necessitating administration by a healthcare professional; development of antibodies to ecallantide that may predispose patients to higher risks of hypersensitivity reactions; and the requirement for a REMS program offer compelling evidence to warrant the continued inclusion of an age criterion. [7]

4 . References

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10. Cicardi M, Zura B. Hereditary angioedema: Pathogenesis and diagnosis. UpToDate Web site. Available at: http://www.uptodate.com/. Accessed July 30, 2019.
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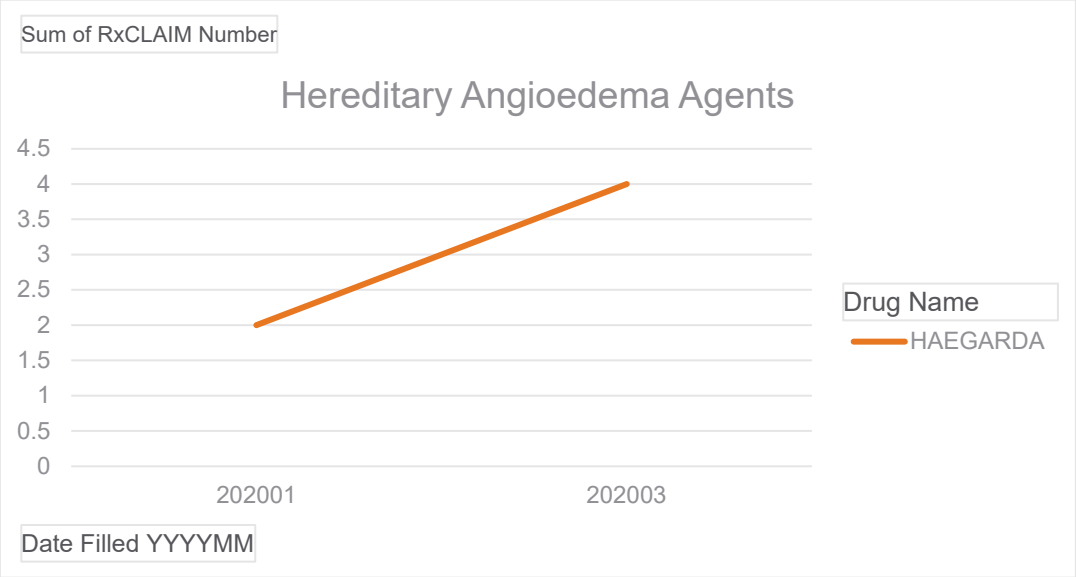
Nevada Medicaid

Hereditary Angioedema Agents
Fee for Service
January 1, 2020 – December 31, 2020

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
HAEGARDA	1	6	180	60



JJ. Hereditary Angioedema Agents

Therapeutic Class: Hereditary Angioedema Agents
Last Reviewed By DUR Board: July 25, 2013

Hereditary angioedema agents are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Approval will be given if all the following criteria are met and documented:

a. Cinryze® (C1 esterase inhibitor)

The recipient must meet all of the following:

1. The recipient has a diagnosis of hereditary angioedema; and

2. The medication is being prescribed by or in consultation with an allergist or immunologist; and

3. The medication is being used as prophylaxis for hereditary angioedema attacks; and

4. The recipient has experienced an inadequate response or adverse event with an attenuated androgen (e.g. danazol, stanozolol) or antifibrinolytic (e.g. tranexamic acid, aminocaproic acid) agent or has a contraindication to all agents in these classes; and

5. The recipient routinely experiences more than one hereditary angioedema attack per month, or the recipient has a history of laryngeal attacks.

b. Berinert® (C1 esterase inhibitor), Kalbitor® (ecallantide) and Firazyr® (icatibant)

The recipient must meet all of the following:

1. The recipient has a diagnosis of hereditary angioedema; and

2. The medication is being prescribed by or in consultation with an allergist or immunologist; and

3. The medication is being used to treat acute hereditary angioedema attacks.

2. Prior Authorization Guidelines

   a. Initial prior authorization approval will be for six months.

   b. Prior authorization requests for continuation therapy will be approved for one year.

   c. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

INTRODUCTION

- Hereditary angioedema (HAE) is a rare disease which affects 1 in 10,000 to 50,000 people worldwide and approximately 6,000 to 10,000 patients in the United States (U.S.). It is characterized by recurrent episodes of localized subcutaneous or submucosal edema lasting for 2 to 5 days that can be disabling and, in the case of laryngeal attacks, life-threatening (*Busse et al 2021, Craig et al 2018, Zuraw 2018, Zuraw and Christiansen 2016).*
  - All ethnicities and races are affected by HAE. The literature reports a female predominance, as women tend to be more symptomatic than men due to hormonal factors related to puberty, contraception, and pregnancy (*Food and Drug [FDA] FDA Multi-discipline Review [Takhzyro] 2018).* HAE is an autosomal dominant disease, and most patients with HAE have a positive family history of angioedema. However, approximately 25% of cases result from *de novo* mutations (*Zuraw 2018*).
  - For the majority of patients, HAE first presents in childhood between 8 to 12 years of age, worsens around puberty, and persists throughout life with fluctuating severity of disease over time (*Busse et al 2021, Farkas et al 2017, Zuraw and Christiansen 2016*).
  - The mortality rate for patients with HAE, despite effective therapies, has been estimated to be as high as 13%. In undiagnosed laryngeal edema cases, mortality can be as high as 30 to 40%. Almost 80% of patients with HAE will experience an abdominal attack, which can be debilitating (*FDA Summary Basis for Regulatory Action [Cinryze] 2018, Zuraw and Farkas 2020a*).
  - HAE is predominantly facilitated by an excessive production of bradykinin, a potent vasodilatory peptide which mediates swelling in HAE through vasodilation and vascular leakage and is thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. Component 1 esterase inhibitor (C1-INH) controls bradykinin production through inhibition of key steps in the coagulation system (*Banerji et al 2017, Busse et al 2021, Lumry 2018, Zuraw 2018*).
    - HAE due to C1-INH deficiency (HAE-C1INH) accounts for the majority of HAE cases and includes 2 subtypes that are clinically indistinguishable: type I HAE (85% of HAE cases) with low C1-INH antigenic and functional levels, and type II HAE (15% of HAE cases) with normal C1-INH antigenic levels but decreased C1-INH functional levels (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw 2018, Zuraw et al 2013a*).
- The frequency and severity of HAE attacks are highly variable and unpredictable, but attacks typically follow a predictable course: swelling that increases slowly and continuously for 24 hours and then gradually subsides over the next 48 to 72 hours (*Craig et al 2018, Zuraw 2018, Zuraw and Christiansen 2016)*.
  - Mild trauma, including dental work, is a common trigger for angioedema episodes in many patients, while tooth extraction and oral surgery are common triggers for laryngeal attacks. Other reported triggers include angiotensin-converting enzyme (ACE) inhibitors, estrogen-containing medications, febrile illness, stress (either mental or physical), menstruation, and possibly *Helicobacter pylori* infection, excitement, sleep deprivation, cold exposure, prolonged sitting or standing, and ingestion of certain foods (*Busse et al 2021, Maurer et al 2018, Zuraw and Farkas 2020a*).
- This monograph describes the agents used to treat HAE (types I and II), including Berinert (C1 esterase inhibitor [human]), Cinryze (C1 esterase inhibitor [human]), danazol, Firazyr (icatibant), Haegarda (C1 esterase inhibitor [human]), Kalbitor (ecallantide), Orladeyo (berotralstat), Ruconest (C1 esterase inhibitor [recombinant]), and Takhzyro (lanadelumab-flyo).
  - The various HAE agents act on different targets to reduce bradykinin production or its effects, decrease angioedema, and improve outcomes in patients with HAE (*Busse et al 2021, Lumry 2018*).
  - The C1-INH agents (ie, Berinert, Cinryze, Haegarda, and Ruconest) replace the missing or malfunctioning C1-INH protein in patients.
  - Danazol is an anabolic androgen which corrects, partially or completely, the primary biochemical abnormality of HAE by increasing the levels of the deficient C1-INH.
  - Firazyr is a bradykinin B2 receptor antagonist and inhibits bradykinin from binding to the bradykinin B2 receptor.
  - Kalbitor and Orladeyo are plasma kallikrein inhibitors that inhibit the production of bradykinin.

- Takhzyro is a monoclonal antibody and kallikrein inhibitor which decreases plasma kallikrein activity to control excess bradykinin generation in patients with HAE.

- Effective HAE management includes acute treatment to arrest an ongoing attack and prophylactic treatment to prevent or minimize attacks (*Busse et al 2021*, *Farkas et al 2017, Maurer et al 2018*).
  - Berinert, Ruconest, Kalbitor, and Firazyr are indicated for the treatment of acute HAE attacks, and guidelines recommend early treatment with either of these 4 agents for on-demand treatment of acute HAE attacks (*Busse et al 2021*, *Maurer et al 2018*).
  - Cinryze, Haegarda, Orladeyo, Takhzyro, and danazol are indicated for routine prophylaxis against HAE attacks.
    - Cinryze, Haegarda, and Takhzyro are preferred prophylactic therapy options in most circumstances. Decisions regarding use of prophylaxis should be individualized, based on the patient's quality of life and treatment preferences in the context of attack frequency, attack severity, comorbid conditions, and access to emergent treatment (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw et al 2013a*).
    - Long-term prophylaxis with androgen therapy (ie, danazol) is not preferred, due to numerous safety concerns including androgenic, anabolic, and hepatic adverse events (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw et al 2013a*).
    - Orladeyo is the newest agent available for the prophylaxis of HAE attacks and was FDA-approved after the most recent HAE guidelines were published.
- Medispan classes: Androgens-Anabolic; Bradykinin B2 Receptor Antagonists; C1 Esterase Inhibitors; Plasma Kallikrein Inhibitors; Plasma Kallikrein Inhibitors - Monoclonal Antibodies

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Berinert (C1 esterase inhibitor [human])	-
Cinryze (C1 esterase inhibitor [human])	-
danazol	✔
Firazyr (icatibant)	✔
Haegarda (C1 esterase inhibitor [human])	-
Kalbitor (ecallantide)	-
Orladeyo (berotralstat)	-
Ruconest (C1 esterase inhibitor [recombinant])	-
Takhzyro (lanadelumab-flyo)	-

(*Drugs@FDA 2021*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*, *Purple Book 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Routine prophylaxis against HAE attacks	Treatment of acute HAE attacks
Berinert (C1-INH [human])		✔ *
Cinryze (C1-INH [human])	✔ †	
danazol	✔ ¶	
Firazyr (icatibant)		✔ ‡
Haegarda (C1-INH [human])	✔ †	
Kalbitor (ecallantide)		✔ ‖
Orladeyo (berotralstat)	✔ ‖	
Ruconest (C1-INH [recombinant])		✔ §
Takhzyro (lanadelumab-flyo)	✔ ‖	

* In pediatric and adult patients; the safety and efficacy of Berinert for prophylactic therapy have not been established. Berinert is indicated for the treatment of acute abdominal, facial, or laryngeal HAE attacks in pediatric and adult patients.
† In patients ≥ 6 years of age

‡ In adults ≥ 18 years of age
§ In adolescent and adult patients; Ruconest limitation of use: effectiveness was not established in HAE patients with laryngeal attacks.

|| In patients ≥ 12 years of age
¶ Danazol is also indicated for the treatment of endometriosis amenable to hormonal management and for fibrocystic breast disease.

(*Prescribing information: Berinert 2020, Cinryze 2021, danazol 2020, Firazyr 2020, Haegarda 2020, Kalbitor 2020, Orladeyo 2020, Ruconest 2020, Takhzyro 2018*)

Off-label uses of HAE agents:

- Cinryze has been used off-label for treatment of acute HAE attacks (*Zuraw and Farkas 2020b, Zuraw et al 2013a*). However, results from an acute-attack trial for Cinryze were not robust enough for FDA approval (*Zuraw et al 2010a, ViroPharma Press Release 2009*).
- Some experts consider Berinert to be an additional option for long-term prophylaxis due to its long half-life, but data are lacking (*Xu et al 2013*).

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Agents for the on-demand treatment of acute HAE attacks

Berinert

- The efficacy and safety of Berinert were evaluated in a double-blind, placebo-controlled randomized-controlled trial (I.M.P.A.C.T.1) in 125 patients with HAE (*Craig et al 2009, FDA Summary Basis for Regulatory Action [Berinert] 2009*). The trial demonstrated that Berinert was effective in treating acute abdominal and facial HAE attacks. The time to onset of symptom relief was significantly shorter with Berinert 20 units (U)/kg vs placebo (48 minutes vs > 4 hours; p = 0.0016).
  - An open-label extension study of I.M.P.A.C.T.1 (I.M.P.A.C.T.2) concluded that Berinert provided reliable efficacy for successive HAE attacks at any anatomical location in 57 patients (*Craig et al 2011, FDA Summary Basis for Regulatory Action [Berinert] 2009*). The median time to symptom relief was 0.46 hours in the per-subject analysis (range, 0.39 to 0.48 hours) and 0.37 hours in the per-attack analysis (range, 0.25 to 0.50 hours). The median time to complete resolution of all HAE symptoms was 15.48 hours in the per-subject analysis (range, 5.79 to 26.63 hours) and 14.28 hours in the per-attack analysis (range, 8.38 to 28.33 hours).

Firazyr

- Firazyr was evaluated for the treatment of acute HAE attacks in 2 Phase 3, double-blind, multi-center, randomized-controlled trials (FAST-1, n = 56; FAST-2, n = 74) (*Cicardi et al 2010b*). FAST-1 compared Firazyr with placebo while FAST-2 compared Firazyr with tranexamic acid.
  - The primary endpoint was not met in FAST-1, and the FDA questioned the validity of using tranexamic acid as an active control in FAST-2 since its efficacy for treatment of acute HAE attacks has not been established. Consequently, the FDA issued a Complete Response Letter requesting a third controlled study (*ViroPharma Press Release 2009*).
- The FAST-3 Phase 3, double-blind, placebo-controlled randomized-controlled trial evaluated the efficacy of Firazyr for the treatment of acute HAE attacks in 98 patients (*Lumry et al 2011*). The study demonstrated that the median time to 50% reduction in symptom severity was significantly shorter with Firazyr (2.0 hours) vs placebo (19.8 hours; p < 0.001) in patients with cutaneous and/or abdominal attacks. In patients with laryngeal attacks, the median time to 50% reduction in symptom severity was 2.5 hours (95% confidence interval [CI], 1.3 to 3.0) with Firazyr vs 3.2 hours (95% CI, 1.0 to 5.4) with placebo.

Kalbitor

- Kalbitor was evaluated for the treatment of acute HAE attacks in 2 Phase 3, double-blind, placebo-controlled randomized trials (EDEMA3, n = 72; EDEMA4, n = 96) (*Cicardi et al 2010a, Levy et al 2010*). The mean change from baseline in the mean symptom complex severity (MSCS) score 4 hours after treatment was -1.1 (95% CI, -1.4 to -0.8) with Kalbitor vs -0.6 (95% CI, -0.8 to -0.4) with placebo (p = 0.041) in EDEMA3, and -0.8 with Kalbitor vs -0.4 with placebo (p = 0.01) in EDEMA4. A -0.3 change in the MSCS score indicated a minimally important difference in symptom improvement.

Ruconest

- The efficacy of Ruconest for acute HAE attacks was evaluated in 2 similar double-blind, placebo-controlled, randomized trials (Study 1205, n = 38; Study 1304, n = 32) (*Zuraw et al 2010b*). The studies found that the median time to onset of symptom relief was 66 minutes (95% CI, 61 to 122) with Ruconest 100 international units (IU)/kg and 122 minutes (95% CI, 72 to 136) with Ruconest 50 IU/kg, vs 495 minutes (95% CI, 245 to 520) with placebo ($p < 0.001$ and $p = 0.013$, respectively).
  - Open-label extension studies of Studies 1205 (n = 62) and 1304 (n = 57) determined that Ruconest provided reliable efficacy for successive HAE attacks (*Moldovan et al 2012, Riedl et al 2013*). In 1205, the median times to beginning of symptom relief for the first 5 attacks were 37 to 67 minutes, and median times to minimal symptoms for the first 5 attacks were 120 to 244 minutes. In 1304, the median times to the beginning of relief of symptoms for attacks 1 through 5 were 60, 65, 120, 60, and 61 minutes, respectively, and overall sustained relief of symptoms was achieved in 87% of Ruconest-treated patients within 4 hours of treatment.
- Treatment with Ruconest for acute HAE attacks was evaluated in a third double-blind, placebo-controlled, randomized-controlled trial (Study 1310) in 75 patients (*Riedl et al 2014*). The median time to the beginning of symptom relief was 90 minutes (95% CI, 61 to 150) in patients treated with Ruconest vs 152 minutes (95% CI, 93 to "not estimable") in placebo-treated patients ($p = 0.031$).
  - An open-label extension study of Study 1310 in 44 patients concluded that Ruconest was effective in improving symptoms of repeat HAE attacks (*Li et al 2015*). The median time to symptom relief ranged from 75 to 90 minutes, and the median time to minimal symptoms for the first 3 attacks ranged from 243 to 303 minutes.

Comparative Review

- A systematic review compared the efficacy of the treatment of 881 acute laryngeal HAE attacks in 12 studies with various HAE agents, including plasma-derived and recombinant C1-INHs, Firazyr, and Kalbitor (*Bork et al 2016*). Onset of symptom relief was generally achieved with all treatment options within 1 hour after the start of treatment for 60 to 100% of laryngeal attacks. Treatment with the body-weight-adjusted dose of Berinert 20 U/kg provided the shortest median time to onset of symptom relief of 15 minutes, followed by approximately 30 to 45 minutes with fixed doses of Berinert or Firazyr, approximately 1.5 hours with Kalbitor, and 2 hours with Ruconest. The proportion of laryngeal attacks that required re-dosing ranged from 0 to 72%. For the 48 attacks treated with Berinert 20 U/kg, no re-dosing was needed after treatment. The comparative review included mostly open-label prospective studies with various protocols and the differences in endpoint definitions between studies made comparisons difficult; therefore, these results should be considered with caution.

Agents for routine prophylaxis against HAE attacks

Cinryze

- The efficacy of Cinryze for prophylaxis of HAE attacks was evaluated in a 24-week double-blind, placebo-controlled, crossover randomized-controlled trial in 22 patients with HAE (*Zuraw et al 2010a*). Treatment with Cinryze 1000 U every 3 to 4 days reduced the rate of attacks by 50% vs placebo (6.26 vs 12.73, respectively; $p < 0.001$). Treatment with Cinryze also significantly reduced the severity and duration of HAE attacks compared with placebo.
  - A 12-week, open-label, single-arm study evaluated the safety of escalating the dose of Cinryze up to 2500 U. Of 20 patients who initiated treatment with 1500 U of Cinryze in the trial, 13 escalated to 2000 U and 12 escalated to 2500 U based on treatment response. Overall, Cinryze was well-tolerated at all dose levels, and the majority of identified adverse events were mild to moderate (*Bernstein et al 2014*).
  - An open-label extension study of 2.6 years duration evaluated the efficacy of treatment with Cinryze 1000 U every 3 to 7 days for prophylaxis in 146 patients with HAE (*Zuraw et al 2012*). The mean frequency of HAE attacks during the study was 0.47 ± 0.83, a 90.0% reduction from the historical mean frequency of 4.7 ± 5.2 attacks/month. A total of 34.9% of patients had 0 attacks during the study.
- The efficacy of Cinryze for the prophylaxis of HAE attacks in pediatrics was established in an unpublished, dose-ranging, 24-week, Phase 3, multi-center, single-blind, crossover randomized-controlled trial in 12 children 7 to 11 years of age (*Aygören-Pürsün et al 2018, Clinicaltrials.gov Web site, FDA Summary Basis for Regulatory Action [Cinryze] 2018*). Compared to the baseline observational period, treatment with both Cinryze 500 U and 1000 U twice weekly decreased the mean number of HAE attacks per month by 2.6 and 3.0, respectively, with a mean reduction in HAE attacks of 71.1% and 84.5%, respectively. Treatment with both doses of Cinryze over a 3-month period also lessened the severity of attacks and reduced the requirement for acute treatment compared with baseline.

Danazol

- Danazol was evaluated for the prevention of HAE attacks in a double-blind, placebo-controlled study in 9 patients with a total of 93 courses of treatment (*Gelfand et al 1976*). Patients treated with danazol were attack-free 93.6% of the time during a 28-day period vs 2.2% of the time in placebo-treated patients ($p < 0.001$). While treated with danazol, C1-INH levels in patients increased 3- to 4-fold, while complement component 4 (C4) levels rose 15-fold.
  - A systematic review of 43 reports evaluated the effectiveness and safety of the use of androgens for HAE prophylaxis in > 1600 patients. Two small placebo-controlled randomized-controlled trials and various long term open-label trials, most commonly with danazol, demonstrated that treatment with androgens reduced the HAE attack rate and were associated with reduced frequency and severity of acute HAE attacks (*Riedl 2015*).

Haegarda

- The efficacy of Haegarda for prophylaxis of HAE attacks was evaluated in COMPACT, a 32-week Phase 3, double-blind, placebo-controlled, crossover randomized trial in 90 patients with HAE (*Longhurst et al 2017*). Treatment with Haegarda 60 IU/kg subcutaneous (SC) injection twice weekly reduced the rate of attacks by 84%, with a mean difference of -3.51 attacks per month vs placebo (95% CI, -4.21 to -2.81; $p < 0.001$). Treatment with Haegarda also significantly reduced the severity and duration of HAE attacks compared with placebo.
  - Haegarda was also assessed in an open-label, parallel-arm extension of COMPACT, including patients ≥ 6 years of age who had either completed the trial or who were study treatment-naïve (*Craig et al 2019)*. The incidence of adverse events was similar in both Haegarda dose groups (11.3 and 8.5 events per patient-year for 40 and 60 IU/kg, respectively). Median annualized attack rates were 1.3 and 1.0, respectively, and median rescue medication use was 0.2 and 0.0 times per year, for 40 and 60 IU/kg groups.

Orladeyo

- The efficacy and safety of orally administered Orladeyo for prophylaxis of HAE attacks were evaluated in a 24-week Phase 3, double-blind, placebo-controlled, parallel-group, multi-center randomized-controlled trial in 121 patients ≥ 12 years of age with HAE (*FDA Multi-discipline Review [Orladeyo] 2020, Zuraw et al 2020*). Treatment with Orladeyo resulted in a significant reduction in the 28-day HAE attack rate relative to placebo; Orladeyo 150 mg demonstrated a 44.2% reduction (1.31 attacks/28 days; $p < 0.001$) and Orladeyo 110 mg demonstrated a 30.0% reduction (1.65 attacks/28 days; $p = 0.024$) compared to 2.35 attacks/28 days with placebo.
  - The proportion of responders with ≥ 50% reduction in HAE attack rates compared to baseline was statistically significant with Orladeyo vs placebo, at 58% with Orladeyo 150 mg ($p = 0.005$) and 51% with Orladeyo 110 mg ($p = 0.021$). In post-hoc analyses, 50% of patients treated with Orladeyo 150 mg achieved ≥ 70% reduction in HAE attacks from baseline, with a significant benefit vs placebo.

Takhzyro

- The efficacy and safety of Takhzyro for prophylaxis of HAE attacks were evaluated in a 26-week Phase 3, double-blind, placebo-controlled, parallel-group, multi-center randomized-controlled trial in 125 patients ≥ 12 years of age with type I or II HAE (*Banerji et al 2018; FDA Multi-discipline Review [Takhzyro] 2018*). There was a significant reduction in HAE attack rates with Takhzyro vs placebo; the mean number of HAE attacks per month with placebo was 1.97 vs 0.48, 0.53, and 0.26 with Takhzyro 150 mg every 4 weeks, 300 mg every 4 weeks, and 300 mg every 2 weeks, respectively ($p < 0.001$ for all treatment groups). There was also statistically significant improvement in the reduction of the number of HAE attacks requiring acute treatment and the number of moderate or severe HAE attacks with all 3 doses of Takhzyro vs placebo ($p < 0.001$ for all treatment groups).

Comparative Review

- An Institute for Clinical and Economic Review (ICER) and California Technology Assessment Forum (CTAF) final evidence report for Takhzyro in HAE included a comparative clinical effectiveness review of 3 clinical trials to evaluate the comparative safety and efficacy of prophylaxis with Takhzyro, Cinryze, and Haegarda in patients with type I and II HAE (*CTAF 2018*). The review determined that the data for Cinryze and Haegarda demonstrated a high certainty of substantial net health benefit vs no prophylaxis (“A” rating). Due to lack of long-term safety data for Takhzyro, evidence for Takhzyro was rated as promising but inconclusive, demonstrating a moderate certainty of a comparable or substantial net health benefit, and a small (but non-zero) likelihood of a negative net health benefit (“promising but inconclusive [P/I]” rating).

CLINICAL GUIDELINES

- There are various organizations that have published guidelines for the treatment of HAE, including the International World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI), Hereditary Angioedema International Working Group (HAWK), U.S. Hereditary Angioedema Association (HAEA), and Joint Task Force on Practice Parameters (JTFPP) (representing the American Academy of Allergy, Asthma & Immunology [AAAAI]; the American College of Allergy, Asthma & Immunology [ACAAI]; and the Joint Council of Allergy, Asthma and Immunology) (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw et al 2013a*).
- Recent guidelines emphasize that the goals of HAE management are to "normalize" life as much as possible and improve quality of life, and ensure patients are able to engage in all work, school, family, and leisure activities as desired without limitation from angioedema symptoms (*Busse et al 2021, Maurer et al 2018*).
- For acute attacks, there is guideline consensus that patients with HAE should have on-demand access to at least 2 standard doses of an effective HAE-specific agent to treat an attack, including Berinert, Firazyr, Kalbitor, or Ruconest, at all times. All 4 of these on-demand medications are considered very effective and generally safe (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw et al 2013a*).
  - All attacks, irrespective of the location of the swelling or the severity of the attack, should be considered for on-demand treatment and treated as early as possible, as earlier treatment shortens attack duration and improves treatment outcomes (*Busse et al 2021, Maurer et al 2018*).
  - Self-administration of on-demand treatment is strongly recommended whenever feasible, except for Kalbitor, which requires administration by a healthcare provider (*Busse et al 2021, Maurer et al 2018*).
- Short-term (or pre-procedural) prophylaxis is indicated when patients are at increased risk of having an HAE attack associated with known triggers such as invasive dental or medical procedures or stressful life events. C1-INH and anabolic androgens are appropriate therapy options for short-term prophylaxis (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw et al 2013a*).
- The 2020 HAEA guidelines specify the C1-INHs, Cinryze and Haegarda, and Takhzyro as preferred prophylactic therapy options in most circumstances (*Busse et al 2021*).
  - Decisions regarding the use of long-term prophylactic treatment should be individualized, based on the patient's quality of life and treatment preferences in the context of attack frequency, attack severity, comorbid conditions, and access to emergent treatment (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018, Zuraw et al 2013a*).
  - While Cinryze has been shown to be both safe and effective against HAE attacks, repeated intravenous (IV) administration can result in loss of readily accessible veins unless great care is taken to preserve the veins. Indwelling ports are discouraged due to the risk of thrombosis and infection, unless deemed medically necessary (*Busse et al 2021*).
  - Long-term prophylaxis with androgen therapy (ie, danazol) is not preferred, due to numerous safety concerns including androgenic, anabolic, and hepatic adverse events (*Busse et al 2021, Farkas et al 2017, Maurer et al 2018*).
- Orladeyo is the newest agent to be approved by the FDA for the prophylaxis of HAE attacks and is not included in current HAE guideline recommendations. However, the availability of new first-line oral prophylactic medications (eg, Orladeyo) may influence the choice of long-term prophylaxis (*Busse et al 2021*).

SAFETY SUMMARY

C1-INH agents (Berinert, Cinryze, Haegarda, and Ruconest):

- Contraindications:
  - Patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to C1-INH preparations.
  - Ruconest: patients with known or suspected allergy to rabbits and rabbit-derived products.
- Key warnings and precautions:
  - Hypersensitivity: severe hypersensitivity reactions may occur. Epinephrine should be immediately available for treatment of any acute severe hypersensitivity reaction following discontinuation of administration.
  - Thromboembolic events: serious arterial and venous thromboembolic events have been reported at the recommended dose of these products in patients with HAE.
  - Plasma-derived C1-INH agents (Berinert, Cinryze, and Haegarda): Transmissible infectious agents: as these agents are made from human plasma, they may contain infectious agents (eg, viruses, and, theoretically, the Creutzfeldt-Jakob agent).

  - Berinert: laryngeal HAE attacks; following treatment of laryngeal HAE attacks, patients should be advised to immediately seek medical attention.
- Adverse reactions:
  - Berinert: the most serious reported adverse reaction was an increase in the severity of pain associated with HAE. The most common adverse reaction (> 4%) was dysgeusia.
  - Cinryze: the most common adverse reactions (≥ 5%) included headache, nausea, rash, vomiting, and fever.
  - Haegarda: the most common adverse reactions (> 4%) included injection site reaction, hypersensitivity, nasopharyngitis, and dizziness.
  - Ruconest: the serious adverse reaction reported in clinical trials was anaphylactic reaction, while the most common adverse reactions (≥ 2%) included headache, nausea, and diarrhea.

Danazol:

- Contraindications: undiagnosed abnormal genital bleeding; markedly impaired hepatic, renal, or cardiac function; pregnancy; breast-feeding; porphyria; androgen-dependent tumor; active thrombosis or thromboembolic disease and history of such events; and hypersensitivity.
- Boxed warnings:
  - Use of danazol in pregnancy is contraindicated.
  - Thromboembolism, thrombotic and thrombophlebitic events including sagittal sinus thrombosis and life-threatening or fatal strokes have been reported.
  - Peliosis hepatis and benign hepatic adenoma have been observed with long-term use. Peliosis hepatis and hepatic adenoma may be silent until complicated by acute, potentially life-threatening intra-abdominal hemorrhage.
  - Danazol has been associated with several cases of benign intracranial hypertension (also known as pseudotumor cerebri).
- Key warnings and precautions: lipoprotein alterations, androgenic effects, porphyria, fluid retention, and hepatic dysfunction.
- Adverse reactions:
  - Androgen-like effects including weight gain, acne, and seborrhea.
  - Possible endocrine effects including menstrual disturbances.
  - Flushing, sweating, vaginal dryness and irritation, and reduction in breast size due to estrogen lowering.
  - Hepatic dysfunction; serious hepatic toxicities including cholestatic jaundice, peliosis hepatis, and hepatic adenoma have been reported.
  - Abnormalities in laboratory tests including creatine phosphokinase, glucose tolerance, glucagon, thyroid binding globulin, sex hormone binding globulin, other plasma proteins, lipids, and lipoproteins.
- Drug interactions:
  - Prolongation of prothrombin time may occur in patients stabilized on warfarin.
  - Increased in levels of carbamazepine, cyclosporine, and tacrolimus.
  - Insulin resistance; caution is advised when administered with antidiabetic drugs.
  - Increased calcemic response to synthetic vitamin D analogs in primary hypoparathyroidism.
  - Myopathy and rhabdomyolysis risk is increased by concomitant administration of danazol with statin agents.

Firazyr:

- Warnings/precautions: laryngeal HAE attacks; following treatment of laryngeal HAE attacks, patients should be advised to immediately seek medical attention.
- Injection site reaction was the most commonly reported adverse reaction and occurred in almost all patients (97%) in clinical trials. Other common adverse reactions (> 1%) included pyrexia, transaminase increase, dizziness, and rash.
- Drug interactions: Firazyr may attenuate the antihypertensive effect of ACE inhibitors. Clinical trials to date have excluded subjects taking ACE inhibitors.
- Firazyr is Pregnancy Category C.

Kalbitor:

- Contraindication: patients with known hypersensitivity to Kalbitor.
- Boxed warning: anaphylaxis has been reported after administration of Kalbitor. Due to this risk, Kalbitor should only be administered by a health care professional with appropriate medical support to manage anaphylaxis and HAE.
- The most common adverse reactions (≥ 3%) included headache, nausea, diarrhea, pyrexia, injection site reactions, and nasopharyngitis.
- Kalbitor is Pregnancy Category C.

Orladeyo:

- Warnings/precaution: additional doses or dosages > 150 mg once daily may increase risk of QT prolongation.
- The most common adverse reactions (≥ 10%) included abdominal pain, vomiting, diarrhea, back pain, and gastroesophageal reflux disease.
- Drug interactions: Dose reductions are recommended in patients with chronic administration of inhibitors of P-glycoprotein or breast cancer resistance protein. P-glycoprotein inducers may decrease Orladeyo plasma concentration. Orladeyo at a dose of 150 mg is a moderate inhibitor of cytochrome P450 (CYP) 2D6 and CYP3A4; concomitant medications with a narrow therapeutic index that are predominantly metabolized by these enzymes should be appropriately monitored.
- In accordance with the FDA's Pregnancy and Lactation Labeling Rule, Orladeyo is not currently assigned a Pregnancy Category. The product prescribing information should be consulted for details.

Takhzyro:

- Warnings/precautions: hypersensitivity reactions have been observed.
- The most common adverse reactions (≥ 5%) included injection site reactions, upper respiratory infections, headache, rash, myalgia, dizziness, and diarrhea.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Berinert (C1 esterase inhibitor [human])	Injection	IV	One dose as needed to treat an acute HAE attack	• May be self-administered
Cinryze (C1 esterase inhibitor [human])	Injection	IV	Every 3 or 4 days	• May be self-administered
Danazol	Capsules	oral	Two or 3 times daily	• May be self-administered • Daily doses > 200 mg are not recommended for long-term use due to risk of adverse reactions (*Zuraw and Farkas 2021*).
Firazyr (icatibant)	Injection	SC	One dose as needed to treat an acute HAE attack; additional doses may be administered at intervals of at least 6 hours with no more than 3 doses in a 24-hour period	• May be self-administered
Haegarda (C1 esterase inhibitor [human])	Injection	SC	Every 3 or 4 days	• May be self-administered
Kalbitor (ecallantide)	Injection	SC	One dose as needed to treat an acute HAE attack; if an attack persists, 1 additional dose may be administered within a 24-hour period	• Should only be administered by a health care professional with appropriate medical support to manage anaphylaxis and HAE.
Orladeyo (berotralstat)	Capsules	oral	Once daily with food	• Dose reductions are recommended in patients with moderate or severe hepatic impairment, patients with chronic administration of P-glycoprotein or breast cancer resistance protein inhibitors,

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				and patients with persistent gastrointestinal reactions. • Should not be used in patients with end-stage renal disease.
Ruconest (C1 esterase inhibitor [recombinant])	Injection	IV	One dose as needed to treat an acute HAE attack; if an attack persists, 1 additional dose may be administered within a 24-hour period	• May be self-administered
Takhzyro (lanadelumab-flyo)	Injection	SC	Every 2 weeks; 4-week dosing may be considered if the patient is well-controlled (eg, attack free) > 6 months	• May be self-administered

See the current prescribing information for full details.

CONCLUSION

- HAE is a rare condition characterized by recurrent episodes of angioedema that may be disabling and, in the case of laryngeal attacks, life-threatening. Various agents are indicated for on-demand and prophylactic treatment of HAE, with a range of pathophysiological approaches. Head-to-head trials between the agents are lacking. Patient- and medication-specific factors should be considered when designing individualized treatment plans for patients with HAE.
- The plasma-derived (human) C1-INH Berinert, recombinant C1-INH Ruconest, the plasma kallikrein inhibitor Kalbitor (ecallantide), and the bradykinin B2 receptor antagonist Firazyr (icatibant), are indicated for acute treatment of HAE attacks and have been shown to be effective in placebo-controlled randomized-controlled trials.
  - Consensus guidelines recommend that patients should have access to an on-demand HAE-specific agent at all times. All 4 FDA-approved on-demand medications are considered very effective and generally safe.
  - Berinert is the only on-demand agent indicated for the treatment of acute abdominal, facial, or laryngeal HAE attacks, as well as the only on-demand agent indicated in pediatric and adult patients.
  - Berinert and Ruconest may be self-administered, via IV injection.
  - Firazyr may be self-administered via SC injection and has a high risk of injection site reactions.
  - Kalbitor has a boxed warning for anaphylaxis and requires administration by a health care professional.
- The plasma-derived (human) C1-INH agents Cinryze and Haegarda, the monoclonal antibody Takhzyro (lanadelumab-flyo), the plasma kallikrein inhibitor Orladeyo (berotralstat), and the anabolic androgen danazol are indicated for routine prophylaxis against HAE attacks.
  - Guidelines recommend Cinryze, Haegarda, and Takhzyro as the preferred prophylactic therapy options in most circumstances.
    - Orladeyo is the newest HAE agent approved by the FDA and is not included in current HAE guideline recommendations.
  - In clinical trials, Takhzyro, Haegarda, and Orladeyo reduced HAE attacks rates up to 87%, 84% and 44%, respectively, compared with placebo; Cinryze reduced rates by 90% compared with historical mean.
  - Cinryze and Haegarda are both indicated in children ≥ 6 years of age; Orladeyo and Takhzyro are indicated in patients ≥ 12 years of age.
  - Haegarda is self-administered via SC injection every 3 to 4 days, while Takhzyro is self-administered via SC injection every 2 to 4 weeks. Cinryze is self-administered via IV injection. Orladeyo capsules are orally administered once daily with food.
  - Orladeyo has a warning and precaution for an increase in QT prolongation at dosages greater than the recommended daily dose; common adverse reactions include gastrointestinal effects. Orladeyo is associated with various drug-drug interactions.
  - Long-term prophylaxis with oral androgen therapy (ie, danazol) is not recommended, due to numerous safety concerns including androgenic, anabolic, and hepatic adverse events.

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Prior Authorization Guideline

Guideline Name Platelet Inhibitors

1 . Criteria

Product Name: Brilinta (ticagrelor)	
Approval Length	1 year(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient has a diagnosis of Acute Coronary Syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction)

AND

2 - The recipient does not have an active pathological bleed or history of intracranial hemorrhage

AND

3 - The recipient will be receiving concomitant treatment with aspirin in a dose of < 100 mg/daily

AND

4 - One of the following:

4.1 The recipient has been started and stabilized on the requested medication

OR

4.2 The recipient has experienced an adverse event with or has an allergy or contraindication to clopidogrel

OR

4.3 Clinically appropriate rationale is provided for why clopidogrel cannot be used (pharmacist review)

Product Name: Generic prasugrel, Brand Effient	
Approval Length	1 year(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient has a diagnosis of Acute Coronary Syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction or ST elevation myocardial infarction)

AND

2 - The recipient does not have an active pathological bleed or history of transient ischemic attack or cerebral vascular accident (CVA)

AND

3 - The recipient will be receiving concomitant treatment with aspirin in a dose of < 100 mg/daily

AND

4 - The recipient has a history of percutaneous coronary intervention

AND

5 - One of the following:

5.1 The recipient has been started and stabilized on the requested medication

OR

5.2 The recipient has experienced an adverse event with or has an allergy or contraindication to clopidogrel

OR

5.3 Clinically appropriate rationale is provided for why clopidogrel cannot be used (pharmacist review)

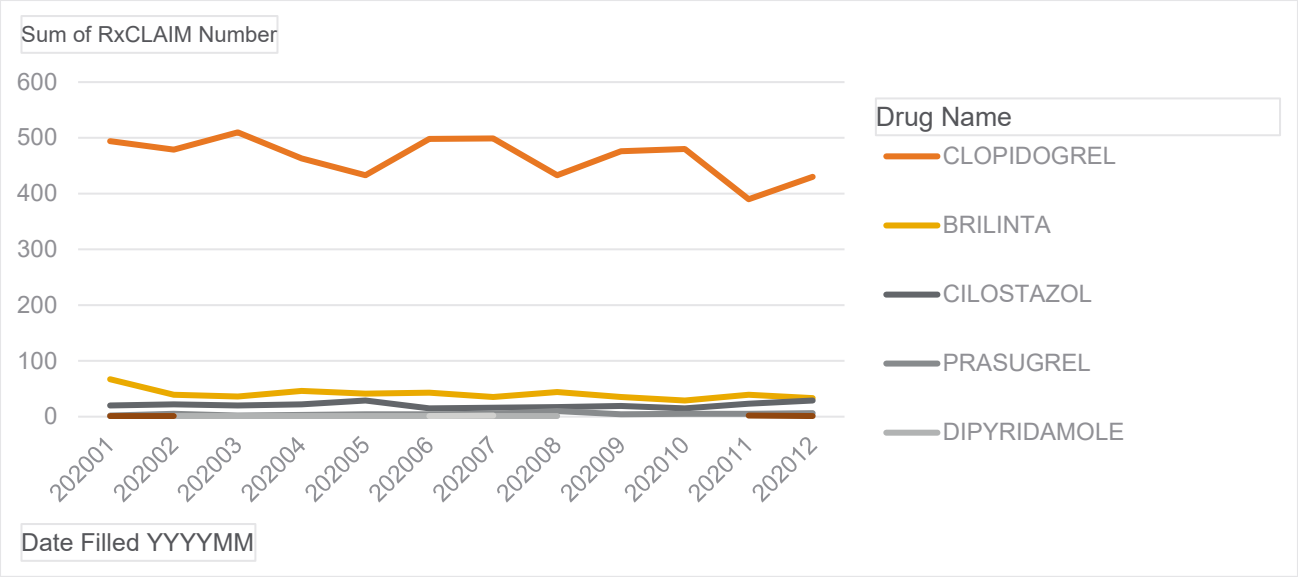
Nevada Medicaid

Platelet Inhibitors

Fee for Service

January 1, 2020 – December 31, 2020

Drug Name	Members	Count of Claims	Total Days Supply	Total Quantity
AGGRENOX	1	1	90	180
ANAGRELIDE HYDROCHLORID	1	1	1	2
ASPIRIN/DIPYRIDAMOLE ER	1	3	184	368
BRILINTA	131	487	16,096	31,869
CILOSTAZOL	71	247	9,291	17,414
CLOPIDOGREL	1,422	5,585	238,883	239,063
DIPYRIDAMOLE	1	8	240	960
EFFIENT	4	6	95	95
KENGREAL	1	1	1	1
PLAVIX	2	7	630	630
PRASUGREL	16	55	2,194	2,194



NN. Platelet Inhibitors

Therapeutic Class: Platelet Inhibitors
Last Reviewed by the DUR Board: January 23, 2014

Brilinta® (ticagrelor) and Effient® (prasugrel) are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Authorization will be given if the following criteria are met and documented:

a. Brilinta® (ticagrelor)

1. The recipient has a diagnosis of Acute Coronary Syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction or ST elevation myocardial infarction); and

2. The recipient does not have an active pathological bleed or history of intracranial hemorrhage; and

3. The recipient will be receiving concomitant treatment with aspirin in a dose of <100 mg/daily; and

4. The recipient has been started and stabilized on the requested medication; or

5. The recipient has experienced an adverse event with or has an allergy or contraindication to clopidogrel; or

6. Another clinically appropriate rationale is provided for why clopidogrel cannot be used.

b. Effient® (prasugrel)

1. The recipient has a diagnosis of ACS (unstable angina, non-ST elevation myocardial infarction or ST elevation myocardial infarction); and

2. The recipient does not have an active pathological bleed or history of transient ischemic attack or cerebral vascular accident (CVA); and

3. The recipient will be receiving concominant treatment with aspirin in a dose of <100 mg/daily; and

4. The recipient has a history of percutaneous coronary intervention; and

5. The recipient has been started and stabilized on the requested medication; or

6. The recipient has experienced an adverse event with or has an allergy or contraindication to clopidogrel; or

7. Another clinically appropriate rationale is provided for why clopidogrel cannot be used.

2. Prior Authorization Guidelines

a. Prior authorization approval will be for one year.

b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Platelet Aggregation Inhibitors

INTRODUCTION

- Cardiovascular (CV) disease is the underlying cause of approximately 17.8 million deaths globally on an annual basis according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2020 update. Stroke also causes significant morbidity and mortality. Stroke is the fifth leading cause of death after heart disease, cancer, unintentional injuries/accidents, and chronic lower respiratory disease. Each year, about 795,000 people experience a new or recurrent stroke (*Virani et al 2020*).
- Platelet inhibitors play a major role in the management of CV, cerebrovascular, and peripheral vascular diseases. These agents are indicated for a variety of Food and Drug Administration (FDA)-approved indications including treatment and/or prevention of acute coronary syndromes (ACS) (myocardial infarction [MI], unstable angina [UA]), stroke/transient ischemic attack [TIA], intermittent claudication, prevention of postoperative thromboembolic complications, thrombocythemia, and valvular heart disease. The use of these agents as both monotherapy or combination therapy by national and international clinical guidelines is based on the specific clinical indication and the patient's risk for thromboembolic events (*Aboyans et al 2018, Amsterdam et al 2014, Anderson et al 2013, Baumgartner et al 2017, Bushnell et al 2014, Culebras et al 2014, Fihn et al 2012, Gerhard-Herman et al 2016, Guyatt et al 2012, Ibanez et al 2018, January et al 2014, January et al 2019, Jauch 2013, Kernan et al 2014, Knuuti et al 2020, Lansberg et al 2012, Levine et al 2011, Levine et al 2016a, Levine et al 2016b, Lip et al 2018, Meschia et al 2014, Nishimura, 2017, O'Gara et al 2013, Powers et al 2015, Powers et al 2018, Powers et al 2019, Smith et al 2011, Smith et al 2017, Valgimigli et al 2018*).
- The platelet inhibitors exert their pharmacologic effects through several different mechanisms of action and have characteristics that distinguish agents from one another.
  - Aspirin (ASA), a salicylate, causes irreversible inhibition of platelet cyclooxygenase, which prevents the formation of thromboxane A2, a platelet aggregate and potent vasoconstrictor. Its use has been the cornerstone of acute treatment for over 15 years; however, evidence from clinical trials demonstrates that ASA reduces adverse clinical events among a broad group of patients treated for both acute and chronic vascular disease (*Harrington et al 2008*).
    - Omeprazole, a component of Yosprala (ASA delayed-release [DR]/omeprazole), in combination with ASA, is an antisecretory compound, which suppresses gastric acid secretion by inhibiting the $[H^+/K^+]$-ATPase enzyme system of the gastric parietal cells. Omeprazole has been characterized as a gastric acid-pump inhibitor as it blocks the final step of gastric acid production, and inhibits both basal and stimulus-induced acid secretion.
  - Zontivity is unique to the class as a selective antagonist of the protease-activated receptor-1 (PAR-1), a primary thrombin receptor, and should only be used with ASA and/or Plavix (clopidogrel) according to their indication or standards of care.
  - Plavix, Effient, and Brilinta inhibit $P2Y_{12}$, an adenosine phosphate receptor on the surface of platelets. Brilinta is the only reversible inhibitor of $P2Y_{12}$ and unlike Plavix does not require hepatic activation. Plavix has a slower onset of action, incomplete platelet inhibition, and poor response in certain patients including those with CYP2C19 polymorphisms. Compared to Plavix, the benefits of Effient have been seen as early as 3 days. Effient and Zontivity are both contraindicated in patients with a history of TIAs.
  - Agrylin has multiple mechanisms in which it exerts its action and is unique in class as it has the ability to reduce platelet counts without affecting white or red blood cell counts.
  - Cilostazol reversibly inhibits platelet aggregation through cyclic AMP phosphodiesterase inhibition. Cilostazol also has vasodilating activity, which has benefits in treating certain diseases.
  - Dipyridamole is a non-nitrate coronary vasodilator that also inhibits platelet aggregation. The mechanism of action of dipyridamole may involve its ability to vasodilate and to increase concentrations of adenosine, a platelet aggregation inhibitor.
- Products included in this class review include Agrylin (anagrelide), Aggrenox (ASA/extended-release [ER] dipyridamole), Brilinta (ticagrelor), cilostazol, Plavix (clopidogrel), dipyridamole, Durlaza (ASA ER), Effient (prasugrel), Yosprala (ASA DR/omeprazole), and Zontivity (vorapaxar). Other platelet aggregation inhibitors used only in inpatient acute care

settings, such as the glycoprotein IIb/IIIa inhibitors and Kengreal (cangrelor); and convenience kits such as clopidogrel 75 mg/ASA 81 mg are not discussed in this review.

- Medispan Class: Platelet Aggregation Inhibitors – Platelet Aggregation Inhibitors, Platelet Aggregation Inhibitors Combinations, Protease-Activated Receptor-1 (PAR-1) Antagonists, Direct-Acting $P2Y_{12}$ Inhibitors, Dipyridamole, Quinazoline Agents, Thienopyridine Derivatives, and Aspirin (Platelet Aggregation Inhibitor).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-Entity Agents	
Agrylin (anagrelide)	✔
Durlaza (aspirin ER)	-
Plavix (clopidogrel)	✔
cilostazol	✔
dipyridamole	✔
Effient (prasugrel)	✔
Brilinta (ticagrelor)	-*
Zontivity (vorapaxar)	-
Combination Products	
Aggrenox (aspirin/dipyridamole ER)	✔
Yosprala (aspirin DR/omeprazole)	✔

* Although generic ticagrelor has been approved by the FDA, the generic product has not been launched.

(*Drugs@FDA.gov 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Agrylin (anagrelide)	cilostazol	Plavix (clopidogrel)	dipyridamole	Effient (prasugrel)	Brilinta (ticagrelor)	Zontivity (vorapaxar)	Durlaza (aspirin ER)	Aggrenox (aspirin/ dipyridamole ER)	Yosprala (aspirin DR/ omeprazole)
Treatment of patients with thrombocythemia, secondary to myeloproliferative neoplasms, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombohemorrhagic events	✔ *									
Reduce the risk of death and MI in patients with chronic coronary artery disease (CAD), such as patients with a history of MI or UA pectoris or with chronic stable angina, and to reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or TIA								✔ †		
Reduction of symptoms of intermittent claudication, as demonstrated by an increased walking distance		✔								
Recent MI, recent stroke, or established peripheral arterial disease (PAD)			✔ ‡							
Reduce the rate of thrombotic CV events in patients with ACS			✔ ‡§							
Prevention of postoperative thromboembolic complications of cardiac valve replacement				✔ ‖						
Reduce the rate of thrombotic CV events in patients with ACS who are being managed with percutaneous coronary intervention (PCI)					✔ ¶					
Reduce the rate of CV death, MI, and stroke in patients with ACS or a history of MI. Also reduces the rate of stent thrombosis in patients who have been stented for the treatment of ACS						✔ #				
Reduce the risk of a first MI or stroke in patients with CAD at high risk for such events						✔ §§				
Reduce thrombotic CV events in patients with a history of MI or with PAD							✔ ††			
Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis									✔	
ASA component: Reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, reducing the combined risk of death and nonfatal MI in patients with previous MI or UA pectoris, reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris, and for patients who have undergone coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) when there is a pre-existing condition for which ASA is already indicated. Omeprazole component: Decrease the risk of developing ASA-associated gastric ulcers in at-risk patients due to age (≥55 years) or documented history of gastric ulcers.										✔ †**

* Approved in adult and pediatric patients (studied in patients aged ≥ 7 years).
† Not indicated for use in situations where a rapid onset of action is required (such as acute treatment of MI or before PCI).
‡ Plavix has been shown to reduce the rate of MI and stroke.
§ For patients with non-ST-elevation ACS (UA/non-ST-elevation myocardial infarction [NSTEMI]), including patients who are to be managed medically and those who are to be managed with coronary revascularization, and for patients with ST-elevation myocardial infarction (STEMI). Plavix should be administered in conjunction with ASA.
‖ As an adjunct to coumarin anticoagulants.
¶ Patients who are to be managed with PCI as follows: patients with UA or NSTEMI and patients with STEMI when managed with primary or delayed PCI.

Administer with a daily maintenance dose of ASA of 75 to 100 mg. For at least the first 12 months following ACS, it is superior to Plavix.
†† Has only been studied as an addition to ASA and/or Plavix. There is limited experience with other antiplatelet drugs or with Zontivity as monotherapy.
** Has not been shown to reduce the risk of gastrointestinal (GI) bleeding due to ASA.
§§Administer with a daily maintenance dose of ASA of 75 to 100 mg. While use is not limited to this setting, efficacy was established in a population with type 2 diabetes mellitus.

(*Prescribing information: Aggrenox 2019, Agrylin 2020, Brilinta 2020, Cilostazol 2020, Durlaza 2015, Effient 2019, Persantine 2019, Plavix 2019, Yosprala 2018, Zontivity 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Antiplatelet therapy plays an important role in the long-term prevention of stroke or TIAs. In a large, meta-analysis (MA) of patients with a previous MI, acute MI, previous TIA/stroke, and acute stroke, as well as patients with an increased risk of atherothrombotic events, it was demonstrated that overall, antiplatelet therapy reduced the odds of the composite outcome of stroke, MI, or vascular death in secondary prevention by approximately 25%. With regard to individual endpoints, antiplatelet therapy reduced the odds of nonfatal MI by 34%, nonfatal stroke by 25% and vascular death by 15% (*Antithrombotic Trialists' Collaboration 2002*).
- There are few head-to-head studies comparing the various antiplatelet agents. In 2013, the Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review (SR) of antiplatelet and anticoagulant treatments. The study authors concluded that Effient reduced rates of CV death, MI or stroke at 30 days in patients undergoing early invasive treatments when compared to Plavix and in UA/NSTEMI patients after 1 year, as did Plavix and Brilinta (*Melloni et al 2013*). Another SR of large, quality trials observing dual antiplatelet therapy (DAPT) of Plavix, Effient, or Brilinta plus ASA when compared to ASA monotherapy found DAPT with Effient or Brilinta and ASA vs DAPT with Plavix and ASA was not associated with a risk reduction of stroke. The authors also noted conflicting results within trials (*Gouya et al 2014*). A double-blind (DB), randomized controlled trial (RCT) compared the efficacy of Brilinta vs Plavix to lower the risk of CV death, MI, or ischemic stroke in 13,885 patients with symptomatic PAD, with a median follow-up of 30 months. The primary efficacy endpoint occurred in 10.8% of patients receiving Brilinta vs 10.6% receiving Plavix (hazard ratio [HR] 1.02; 95% confidence interval [CI], 0.92 to 1.13; p = 0.65). Major bleeding occurred at the same frequency with both treatments (1.6%), and Brilinta was discontinued more often than Plavix, mainly due to dyspnea (4.8 vs 0.8%) (*Hiatt et al 2017*).
- Recently, network MAs assessing the use of $P2Y_{12}$ inhibitors in ACS have been conducted (*Baldetti et al 2020, Navarese et al 2020*). Baldetti and colleagues performed a network MA of 14 studies involving 145,019 patients (*Baldetti et al 2020*). Endpoints included MACE, all-cause death, MI, definite stent thrombosis, and major bleeding at 30 days and 1 year all-cause death and MI. Results revealed that Effient had the highest efficacy in reducing adverse outcomes in patients with ACS and the highest probability of being the best $P2Y_{12}$ inhibitor to reduce hard adverse events at 30 day and 1 year follow-up. In a network MA of 52,816 patients from 12 randomized trials, Navarese and colleagues concluded that Effient and Brilinta reduced ischemic events and increased bleeding in comparison with Plavix, a significant CV and all-cause mortality reduction was seen with Brilinta as compared to Plavix, and there was no efficacy and safety difference between Effient and Brilinta (*Navarese et al 2020)*.
- Chiarito and colleagues performed a SR and MA involving 9 randomized trials that compared $P2Y_{12}$ inhibitor monotherapy vs ASA monotherapy for secondary prevention in 42,108 patients with established atherosclerosis (*Chiarito et al 2020*). Results revealed that $P2Y_{12}$ inhibitor monotherapy is associated with comparable risks of all-cause death, vascular death, and stroke, and a marginal risk reduction for MI, as compared to ASA monotherapy in this setting. However, the high number needed to treat and the absence of any major effect on death questions the clinical relevance of the marginally lower risk of MI seen with $P2Y_{12}$ inhibitor monotherapy.
- The CAPRIE study demonstrated that patients with a recent ischemic stroke or MI, or those with symptomatic PAD who were treated with Plavix experienced a 5.32% annual risk of ischemic stroke, MI, or vascular death compared to 5.83% of patients treated with ASA (relative risk reduction [RRR], 8.7% in favor of Plavix; 95% CI, 0.3 to 16.3; p = 0.043) (*Antithrombotic Trialists' Collaboration 2002, CAPRIE 1996*). Results from the MATCH study demonstrated that the addition of ASA to Plavix in high-risk patients with a recent ischemic stroke or TIA was associated with a nonsignificant difference in reducing major vascular events. In this trial, DAPT was associated with more life-threatening, major, and minor bleeds (*Diener et al 2004*). In the ESPRIT study, patients within 6 months of a TIA or minor stroke of presumed arterial origin were randomized to receive ASA with or without dipyridamole. The rate of the primary composite outcome, death from all vascular causes, nonfatal stroke, nonfatal MI, or major bleeding complications (whichever occurred first), was 13% with combination therapy vs 16% with ASA (HR, 0.80; 95% CI, 0.66 to 0.98, absolute risk reduction [ARR], 1% per year; 95% CI, 0.1 to 1.8) (*Halkes et al 2006*). One MA compared DAPT (ASA plus Plavix) with ASA alone in patients with acute minor ischemic stroke or TIA and found that starting DAPT within 24 hours of symptom onset reduced the absolute risk of non-fatal recurrent stroke, but had no impact on all-cause mortality (*Hao et al 2018*). There was a 0.2% absolute increase in moderate or severe extracranial bleeding with DAPT vs ASA alone. The results were similar to 2 MAs for secondary stroke prevention in patients with TIA or ischemic stroke (*Kheiri et al 2018, Ye et al 2019*). Another MA in elderly patients (≥ 65 years) with ischemic stroke or TIA found that DAPT was superior to ASA monotherapy (RR, 0.79; 95% CI, 0.69 to 0.91), but similarly effective for stroke prevention as Plavix monotherapy (RR, 1.01; 95% CI, 0.93

to 1.10) (*Ding et al 2018*). DAPT also doubled the risk for bleeding in elderly compared to younger patients (RR, 2.18; 95% CI, 1.02 to 4.69).

- With regard to the treatment of ACS, in the CLARITY-TIMI 28 study, patients who presented within 12 hours of a STEMI were randomized to receive either Plavix or placebo for 30 days. Treatment with Plavix was associated with a reduction of the composite endpoint of occluded infarct-related artery on angiography, death, or recurrent MI before angiography (*Sabatine et al 2005a*). Patients included in the COMMIT study were admitted within 24 hours of a suspected acute MI and received either combination therapy with Plavix and ASA or ASA monotherapy. In this study, there was a significant reduction in the risk of the composite endpoint of death, re-infarction, or stroke (p = 0.002), and in death from any cause (p = 0.03) in patients receiving combination therapy after 15 days (*COMMIT 2005*). In the CURE study, investigators compared long-term (3 to 12 months) combination therapy with Plavix plus ASA to ASA monotherapy in patients with a NSTEMI who presented within 24 hours of symptom onset. The results demonstrated that combination therapy resulted in a 20% RRR in the composite outcome of nonfatal MI, stroke, or vascular death (p < 0.001). The compelling benefit of combination therapy noted in the CURE study was in the reduction of nonfatal MI. Due to the low number of strokes that occurred during the study, the associated reduction was not significant. There was also a weak trend suggesting the possibility of small reductions in death associated with combination therapy that was not significant (*CURE 2001, Harrington et al 2008, Lansberg et al 2012*). MAs of ACS patients or those undergoing PCI to reduce thrombotic events, have conflicting results. Results reported Plavix was superior to placebo in reducing the risk of CV death and stroke. Effient or Brilinta treatment when compared to Plavix provided additional benefit regarding CV mortality and MI, but no advantage in stroke (*Aradi et al 2013*). A secondary analysis of the TRILOGY ACS trial found intensive antiplatelet therapy with Effient may be beneficial in reducing CV deaths, MIs, or strokes when an angiography is performed prior to treatment and anatomic coronary disease is confirmed (*Roe et al 2012, Wiviott et al 2013*). The CHARISMA study was another long-term trial (median, 28 months) that enrolled and randomized patients with clinically evident CV disease to either combination treatment with Plavix and ASA or to monotherapy with ASA. The rate of the primary composite endpoint of MI, stroke, or death from CV causes was not different between the 2 treatments (6.8 vs 7.3%; relative risk [RR], 0.93; 95% CI, 0.83 to 1.05; p = 0.22) (*Bhatt et al 2006*). There is also limited evidence that Plavix has a greater impact on preventing the composite of CV death, MI, and stroke in smokers compared to non-smokers (*Gagne et al 2013*). A MA evaluated the clinical efficacy and safety of $P2Y_{12}$ inhibitors in patients with STEMI undergoing primary PCI, as defined by composite major adverse CV events (MACE). At 1 month, the analysis suggested that Effient was associated with lower MACE vs Plavix (standard dose odds ratio [OR] 0.59; 95% CI, 0.50 to 0.69) and Brilinta (standard dose OR 0.69; 95% CI, 0.56 to 0.84); lower mortality and MI vs Plavix and standard Brilinta; and lower stroke risk vs standard Plavix and Brilinta. At 1 year, Effient was associated with lower mortality and MACE vs Plavix and Brilinta. In general, Effient and Brilinta were more efficacious vs Plavix in this analysis (*Rafique et al 2016*). However, another network meta-analysis (NMA) evaluated the efficacy of $P2Y_{12}$ inhibitors (Plavix, Effient, Brilinta, and cangrelor) in patients undergoing PCI for any indication (STEMI or non-ST elevated ACS) and did not find any significant differences between any of the agents in terms of all-cause mortality, CV death, MI, probable or definite stent thrombosis, stroke, major bleeding, or MACE (*Westman et al 2017*). When used post fibrinolytic therapy in patients with a STEMI, Brilinta and Plavix demonstrated similar rates of bleeding, MACE, mortality, MI, and stroke in a 2018 MA of 5 RCTs, as well as a 2019 RCT (*Kheiri et al 2019, Berwanger et al 2019*).
- The duration of DAPT has been highly debated and often controversial. Evolving evidence has consistently demonstrated that estimated benefits are accompanied by a certain proportion of risk; therefore, not all patients would benefit from DAPT treatment. To further complicate interpretations, often first-generation stents were studied for DAPT; however, newer stents have improved safety benefits, but studies and analyses often have ≥ 1 methodological limitations. Current evidence includes an analysis of the National Heart, Lung, and Blood Institute (NHLBI) observational registry which followed over 3,000 ACS patients following PCI with a drug-eluting stent (DES); this study found that patients who continued on DAPT (Plavix plus ASA) experienced lower mortality after 1 year, but had a higher risk of repeat PCI within 4 years (*Mulukutala et al 2013*). The PRODIGY trial demonstrated that Plavix plus ASA administered in patients who received a DES or bare metal stent for 24 months was not significantly more effective than a 6-month Plavix regimen in reducing the composite of death due to any cause, MI, or cerebrovascular accident (*Valgimigli et al 2012*). However, the DAPT trial found patients who continued DAPT beyond 1 year after the placement of a DES compared with ASA therapy alone, significantly reduced the risk of stent thrombosis, MACE and cerebrovascular events, including MI; but was associated with an increased risk of bleeding and all-cause mortality (*Mauri et al 2014*). Several MAs/systematic reviews have concluded there is no increased risk of stent thrombosis with shorter duration DAPT, and treatment is associated with a lower risk of bleeding. MAs restricted to predominantly newer generation DES have demonstrated increased trends of increased all-cause mortality associated with prolonged duration of DAPT, although

not all analyses reached statistical significance (*Elmariah et al 2015, Navarese et al 2015, Udell et al 2016, Misumida et al 2018*). Another MA determined that long-term DAPT was associated with a significant decrease in risk of death, MI, and stroke, primarily in patients with prior MI or stroke, but not PAD, while long-term DAPT was also associated with increased major bleeding. Of note, the study was not able to evaluate the impact of DES on atherothrombotic events (*Fanari et al 2017*). Another MA assessed the efficacy and safety of duration of DAPT in patients with implantation of predominantly newer-generation DES. The analysis determined treatment with DAPT for 12 months vs 3 to 6 months resulted in no significant differences in incidences of death, major hemorrhage, or MI. DAPT for 18 to 48 months vs 6 to 12 months was also associated with no difference in incidence of all-cause death, but showed decreased MI and stent thrombosis, and increased major hemorrhage. A risk-benefit analysis found 3 fewer stent thromboses and 6 fewer MIs but 5 more major bleeds per 1,000 patients/year treated with prolonged DAPT. Also, treatment with DAPT > 1 year after MI reduced the composite risk of CV death, MI, or stroke but increased major bleeding (*Bittl et al 2016*).

- A MA of 16 RCTs looking at the effects of antiplatelet agents (eg, ASA, Aggrenox, and ASA plus Plavix) and vitamin K antagonists for the prevention of thrombosis in patients with lower limb atherosclerosis undergoing bypass grafting found therapy with ASA or Aggrenox had an effect on peripheral bypass grafts and prosthetic graft patency, but not venous grafts alone. Treatment with Plavix plus ASA had greater increases of bleeding, but no difference in primary graft patency compared to ASA alone (*Bedenis et al 2015*).
- A major clinical study demonstrating the safety and efficacy of Brilinta is the PLATO study. PLATO was an international, DB, double-dummy (DD), multicenter (MC), RCT that compared Brilinta to Plavix in adult patients hospitalized with documented ACS, with or without ST-segment elevation within the previous 24 hours (n = 18,624). After 12 months, the risk of the primary composite endpoint of vascular death, MI, or stroke was significantly reduced with Brilinta (9.8 vs 11.7%; HR, 0.84; 95% CI, 0.77 to 0.95; p < 0.001). Brilinta also significantly reduced the risk of the secondary endpoints of the composite of all-cause mortality, MI, or stroke (10.2 vs 12.3%; HR, 0.84; 95% CI, 0.77 to 0.92; p < 0.001); the composite of vascular death, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event (14.6 vs 16.7%; HR, 0.88; 95% CI, 0.81 to 0.95; p < 0.001); MI (5.8 vs 6.9%; HR, 0.84; 95% CI, 0.75 to 0.95; p = 0.005), and vascular death (4 vs 5.1%; HR, 0.79; 95% CI, 0.69 to 0.91). Furthermore, Brilinta significantly reduced the risk of all-cause mortality (4.5 vs 5.9%; HR, 0.78; 95% CI, 0.69 to 0.89). Rates of major bleeding were not different between the 2 treatments (p = 0.43) (*Wallentin et al 2009*).
  - Several subanalyses of the PLATO study have been conducted (*James et al 2011, Cannon et al 2010, Steg et al 2010, James et al 2010a, James et al 2010b, Held et al 2011, Wallentin et al 2010, Mahaffey et al 2011, Storey et al 2011, Becker et al 2011, Banerjee et al 2008, Kohli et al 2013, Husted et al 2014, Varenhorst et al 2014, Velders et al 2016*). One subanalysis found Brilinta was associated with fewer first and recurrent composite CV events based on the entire international study population (*Kohli et al 2013*). In patients with ACS undergoing noninvasive (p = 0.045) or invasive procedures (p = 0.0025), Brilinta remained more efficacious compared to Plavix (*James et al 2011, Cannon et al 2010*). However, in patients with ST-elevation or left bundle branch block (p = 0.07), chronic kidney disease (CKD) (p = 0.13), or diabetes (p-value = not reported), and in those who underwent CABG surgery (p = 0.29), there was no difference between Brilinta and Plavix with regard to the primary composite endpoint (*Steg et al 2010, James et al 2010a, James et al 2010b, Held et al 2011*). In patients with or without ST-elevated ACS, gender was not a risk factor for outcomes, but some signals alluded to men benefiting most. The number of primary events that occurred in men was double that of women (*Husted et al 2014*). A genetic substudy was also conducted and demonstrated Brilinta to be more efficacious than Plavix, irrespective of cytochrome P450 2C19 and ABCB1 polymorphisms (p = 0.0380) (*Wallentin et al 2010*). In the original PLATO study, a significantly higher rate of dyspnea was observed with Brilinta; however, data from a substudy revealed Brilinta had no effect on pulmonary function (*Wallentin et al 2009, Storey et al 2011*). In terms of causes of death, Brilinta appeared to have a greater effect on sudden death over Plavix within the study population (*Varenhorst et al 2014*). Another post-hoc subgroup analysis of patients with STEMI treated with primary PCI demonstrated treatment with Brilinta resulted in a reduction of the primary end point compared with Plavix (7.9 vs 8.6%; p = 0.38) (*Velders et al 2016*).
  - Mahaffey et al compared the effects of Brilinta and Plavix among patients enrolled in the PLATO study who were from the United States (U.S.) (N = 1413). The superior benefits of Brilinta in reducing thrombotic CV events were not observed among this specific patient population. Specifically, there was no difference between Brilinta and Plavix in the rate of the primary composite endpoint (11.9 vs 9.5%; HR, 1.27; 95% CI, 0.92 to 7.75; p = 0.15). The authors discussed that among these patients who were treated with Brilinta, the lowest event rates were observed in patients also receiving low-dose ASA maintenance therapy. In contrast, event rates in those treated with Plavix were similar regardless of concurrent high- or low-dose ASA. Despite the potential role that ASA maintenance dosing may play in explaining the regional differences observed within the PLATO study, the authors noted that the pattern of results are

consistent with what might be expected by chance alone in a large, multiregional clinical study with multiple exploratory analyses. A potential mechanism by which high-dose ASA is thought to reduce the effects of Brilinta relates to its ability to inhibit the endothelial release of prostacyclin in a dose-dependent fashion at doses greater than 80 mg/day. Prostacyclin reduces platelet reactivity and may contribute synergistically in vivo to the antiplatelet effects of $P2Y_{12}$ inhibitors. Therefore, the therapeutic effects of a higher mean level of $P2Y_{12}$ inhibition achieved with Brilinta in the PLATO study may be attenuated when endogenous prostacyclin production is inhibited (*Mahaffey et al 2011*). Until a prospective clinical study comparing the effects of low- vs high-dose ASA maintenance therapy and its effect on the efficacy of Brilinta is conducted, it remains unclear as to why the diminished effects of Brilinta in the U.S. population were observed. Of note, the FDA-approved dosing of Brilinta recommends that after the initial loading dose of ASA (325 mg), a daily maintenance dose of ASA of 75 to 100 mg should be used.

- The GLOBAL LEADERS RCT compared DAPT (ASA plus Brilinta) for 1 month followed by Brilinta monotherapy for 23 months vs standard DAPT (ASA plus either Plavix or Brilinta) for 12 months followed by ASA monotherapy for 12 months for patients undergoing PCI with a DES for either CAD or ACS (*Vranckx et al 2018*). After 2 years, there was no differences between groups for the primary composite outcome of all-cause mortality, or non-fatal MI (RR, 0.87; 95% CI, 0.75 to 1.01). A pre-specified ancillary analysis (GLASSY) found that Brilinta monotherapy after 1 month of DAPT was noninferior, but not superior, to standard DAPT in terms of all-cause death, nonfatal MI, nonfatal stroke, or urgent target vessel revascularization (RR, 0.85; 95% CI, 0.72 to 0.99); rates of bleeding were not significantly different between groups (*Franzone et al 2019*).
- The TWILIGHT trial compared DAPT (ASA plus Brilinta) for 3 months followed by Brilinta monotherapy for 12 months vs DAPT (ASA plus Brilinta) for 15 months in patients at high risk for bleeding or ischemic events undergoing PCI with a DES (*Mehran et al 2019*). At 15 months, Brilinta monotherapy was associated with a lower risk of bleeding (HR, 0.56; 95% CI, 0.45 to 0.68) and no increased risk of death, MI, or stroke (HR, 0.99; 95% CI, 0.78 to 1.25).
- In the TICO randomized multicenter trial, 3056 patients with ACS treated with DES were randomized to Brilinta monotherapy 90 mg twice daily after 3 months of DAPT (n = 1527) or Brilinta-based 12-month DAPT (n = 1529) (*Kim et al 2020*). The primary outcome was a 1-year net adverse clinical event, defined as a composite of major bleeding and adverse cardiac and cerebrovascular events. Results revealed that the primary outcome occurred in 59 patients (3.9%) administered Brilinta monotherapy after 3 month DAPT vs 89 patients (5.9%) given Brilinta-based 12-month DAPT (absolute difference: -1.98%; 95% CI, -3.50% to -0.45%; HR, 0.66; 95% CI, 0.48 to 0.95; p = 0.01). Major bleeding occurred significantly less frequently in patients administered Brilinta monotherapy after 3 month DAPT vs Brilinta-based 12 month DAPT (1.7% vs 3%; HR, 0.56; 95% CI, 0.34 to 0.91; p = 0.02); however, the incidence of major adverse cardiac and cerebrovascular events was not significantly different between the groups (2.3% vs 3.4%; HR, 0.69; 95% CI, 0.45 to 1.06; p = 0.09).
- The FDA approval of Brilinta for the reduction in the rate of CV death, MI, and stroke in patients with a history of MI was based on results from the PEGASUS TIMI-54 trial. Approximately 21,000 patients who had a MI at least 1 to 3 years prior and had a high-risk factor for another event were randomized to treatment with Brilinta 90 mg twice daily, 60 mg twice daily, or placebo in addition to ASA 75 to 150 mg and followed for a median time of 33 months. The primary composite endpoint of time to first event of CV death, MI, or stroke was significantly reduced by 16% with Brilinta 60 mg twice daily plus ASA with event rates 1.27% lower at 3 years in the Brilinta 60 mg twice daily plus ASA group compared to those patients treated with ASA alone (p = 0.004) (*Bonaca et al 2015*). Subgroup analyses have also demonstrated similar outcomes for the primary endpoint of MACE between patients with and without diabetes and between patients with and without prior coronary stenting (*Bhatt et al 2016, Furtado et al 2019*). The primary safety endpoint, TIMI major bleeding, was significantly increased with Brilinta treatment but to a lesser degree with the 60 mg twice daily dose (Brilinta 60 mg twice daily plus ASA, 2.3% vs ASA monotherapy, 1.1%; p < 0.001) (*Bonaca et al 2015*). The rates of CV mortality or all-cause mortality alone were not significantly different from ASA monotherapy.
- In a 2018 MA, dual or triple antithrombotic therapy with Brilinta vs Plavix significantly increased the risk of clinically significant bleeding (OR, 1.52; 95% CI, 1.12 to 2.06, and OR, 1.7; 95% CI, 1.24 to 2.33, respectively). Among those on triple therapy, a higher risk of MACE was seen with Brilinta compared to Plavix (OR, 1.88; 95% CI, 1.26 to 2.80); patients who received dual therapy exhibited a similar risk of MACE and stroke (*Andreou et al 2018*).
- A MA comparing Brilinta-based antiplatelet regimens to conventional antiplatelet regimens found that, among patients with CAD, Brilinta demonstrated a lower risk of death (HR, 0.84; 95% CI, 0.77 to 0.91) and MI (HR, 0.87; 95% CI, 0.80 to 0.94) (*Cassese et al 2020*).
- The SOCRATES trial evaluated approximately 13,200 patients with an acute, non-severe ischemic stroke or high-risk TIA who had not received intravenous or intra-arterial thrombolysis, were not considered to have had a cardioembolic

stroke, and were treated with either Brilinta or ASA for 90 days. Brilinta was not significantly superior to ASA in reducing stroke, MI, or death at 90 days, the primary endpoint (6.7% of the Brilinta group vs 7.5% of those treated with ASA; p = 0.07). Additionally, no secondary endpoints were considered significantly different between treatment groups but generally trended towards favoring Brilinta (with the exception of death and CV death). Exploratory analyses indicated that Brilinta may be more effective at 7 days in reducing ischemic stroke and all stroke. However, more patients discontinued treatment in the Brilinta group (17.5%) vs the ASA group (14.7%), mainly due to dyspnea and any bleeding (*Johnston et al 2016*).
    - A subgroup analysis of SOCRATES assessed patients from Asian countries (N = 3858), as the composite of stroke, MI, or death occurred at an increased rate in patients from Asia compared with patients outside of Asia (10.6 vs 5.7%, nominal p < 0.01), with higher incidence of major or minor bleeding events in patients from Asia (2.1 vs 1.2%, respectively). In the patients from Asia, treatment with Brilinta significantly reduced the rate of the composite endpoint compared with ASA treatment (9.6 vs 11.6%; HR, 0.81; 95% CI, 0.67 to 0.99), with no significant differences in the rates of major bleeding between treatment groups (*Wang et al 2017*).
- In the randomized, placebo-controlled (PC), DB, THALES trial, Johnston and colleagues assessed the effects of Brilinta plus ASA vs ASA monotherapy for 30 days in 11,016 patients with a mild to moderate acute noncardioembolic ischemic stroke or TIA who were not undergoing thrombolysis or thrombectomy (*Johnston et al 2020*). Brilinta was administered as a 180 mg loading dose followed by 90 mg twice daily and ASA was given as 300 to 325 mg on the first day followed by 75 to 100 mg daily. The primary outcome was a composite of stroke or death within 30 days; severe bleeding was the primary safety outcome. Results revealed that a primary outcome event occurred in 303 (5.5%) patients in the Brilinta-ASA group vs 362 (6.6%) patients in the ASA monotherapy group (HR, 0.83; 95% CI, 0.71 to 0.96; p = 0.02). Ischemic stroke also occurred less frequently in the combination group (5% vs 6.3%; HR, 0.79; 95% CI, 0.68 to 0.93; p = 0.004). Severe bleeding occurred significantly less in the ASA monotherapy group (7 vs 28 patients; p = 0.001).
- The TiCAB trial compared Brilinta 90 mg twice daily to ASA 100 mg daily in patients undergoing CABG (*Schunkert et al 2019*). Study enrollment was prematurely halted, with only 1859 of the planned 3850 patients enrolled. No significant differences in major CV events or bleeding were demonstrated between the groups, but the study was underpowered to detect between-group differences.
- The THEMIS trial evaluated DAPT with Brilinta plus ASA vs ASA alone in 19,220 diabetic patients with stable CAD (ie, history of PCI or CABG, or documented angiographic stenosis of > 50% in at least 1 coronary artery) (*Steg et al 2019*). Ischemic CV event rates were slightly lower among patients receiving DAPT (HR, 0.90; 95% CI, 0.81 to 0.99), but major bleeding rates were also higher with DAPT (HR, 2.32; 95% CI, 1.82 to 2.94). Adding Brilinta to ASA was not found to have a favorable risk-benefit profile in the overall trial population. A prespecified analysis of patients in the THEMIS trial who had previously undergone PCI (N = 11,154) found that, although major bleeding was still increased (HR, 2.03; 95% CI, 1.48 to 2.76) in this patient population, there may be a net clinical benefit with DAPT (HR, 0.85; 95% CI, 0.75 to 0.95) (*Bhatt et al 2019*).
- The major clinical trial demonstrating the safety and efficacy of Effient for its FDA-approved indication was TRITON-TIMI 38 (N = 13,608). Results demonstrated that Effient was significantly more effective than Plavix in reducing ischemic events in patients with ACS who underwent PCI. However, the trial did not demonstrate a decrease in the mortality rate with Effient. In addition, the results from TRITON-TIMI 38 did show a significantly higher rate of major, minor, life-threatening, and fatal bleeding events with Effient. Of note, certain patient subgroups, specifically those who were ≥ 75 years of age, those weighing < 60 kg and those with a past history of stroke or TIA, did not demonstrate a clinical benefit with Effient (*Wiviott et al 2007*). In addition, several subgroup analyses were also conducted based on TRITON-TIMI 38 and 1 patient subgroup in particular, those with diabetes, were found to have a significantly greater reduction in ischemic events with Effient when compared to nondiabetic patients being treated with either Effient or Plavix (*Antman et al 2008, Montalescot et al 2009, Murphy et al 2008, O'Donoghue et al 2009, Pride et al 2009, Wiviott et al 2008a, Wiviott et al 2008b*).
- In a 2018 MA, adverse CV outcomes were significantly lower with the use of Effient in comparison to Plavix following PCI. In an evaluation of bleeding outcomes, both agents yielded similar rates of major and minor bleeding episodes (*Brundhun et al 2018*).
- One MA compared Brilinta and Effient following PCI, both agents demonstrated similar efficacy in reducing all-cause mortality, MACE, and stroke; however, the risk of major bleeding was higher with Brilinta (OR, 1.57; 95% CI, 1.30 to 1.89) (*Guan et al 2018*). Another MA compared these agents in patients with type 2 diabetes following PCI that failed to find any significant differences between agents for mortality, MACE, MI, stroke, or major bleeding (*Yang et al 2018*). A 2020 SR and MA also compared Brilinta and Effient for DAPT therapy in patients with ACS undergoing PCI and

concluded that there were no significant differences between the agents with regard to MACE, all-cause mortality, CV mortality, MI, stent thrombosis, and bleeding (*Al-Abdouh et al 2020*).

- The ISAR-REACT 5 trial compared Brilinta and Effient in patients (n = 4018) with ACS for whom invasive evaluation was planned (*Schupke et al 2019*). The incidence of the composite primary endpoint (death, MI, or stroke at 1 year) was significantly higher in the Brilinta group (HR, 1.36; 95% CI, 1.09 to 1.70); major bleeding was not significantly different between groups.
- Another MA compared antiplatelet agents (Brilinta and Effient) to Plavix in patients with CKD and ACS. The other antiplatelets were associated with a reduced risk of MACE (HR, 0.88; 95% CI, 0.79 to 0.99) and no difference in bleeding vs Plavix (*Bonello et al 2018*).
- As concluded in the TRILOGY ACS study, in patients with UA/NSTEMI who do not undergo revascularization, when added to ASA therapy, Effient did not significantly reduce the frequency of death from CV causes, MI, or stroke, as compared with DAPT with Plavix and ASA, and similar risks of bleeding were observed (*Kohli et al 2014, Roe et al 2012*). However, a secondary analysis of patients who underwent angiography prior to Effient treatment experienced fewer CV deaths, MIs, or strokes than those who were in the Plavix arm (*Roe et al 2012, Wiviott et al 2013*).
- First-in-class PAR-1 antagonist, Zontivity, was FDA-approved based on a post-hoc analysis of patients with a history of MI or PAD who were taking ASA and/or a thienopyridine (mainly Plavix) concomitantly. A safety review terminated the full TRACER trial and patients with stroke in the TRA 2°P-TIMI 50 trial due to significantly increased risks for bleeding, including intracranial hemorrhage (ICH). Both trials were PC. In the TRA 2°P-TIMI 50 trial, Zontivity demonstrated effectiveness in the secondary prevention of CV events, mainly MI and the composite endpoint of CV death, MI, or stroke, primarily driven by the reduction in MI. Although TRA 2°P-TIMI 50 was not designed to evaluate the benefits and risks of Zontivity in individual patient subgroups, an analysis of patients who were comprised of post-MI and PAD without a history of stroke or TIA was evaluated by the FDA for approval. Those results showed three-year Kaplan Meier (K-M) event rate for the primary efficacy endpoint of 7.9% in the Zontivity group compared to 9.5% in the placebo group (HR, 0.8; 95% CI, 0.73 to 0.89; p < 0.001). The benefit of Zontivity is tempered by the significant increase of bleeding with Zontivity use compared to placebo. Significantly increased bleeding rates were also observed in the TRA 2°P-TIMI 50 trial for GUSTO moderate or severe bleeding, TIMI clinically significant bleeding, and GI bleeding (NNH = 97, 25, 98, respectively). However, there was no significant difference between placebo and Zontivity for fatal bleeds (*Morrow et al 2012, Tricoci et al 2012, FDA Summary Review [Zontivity] 2014, FDA Advisory Committee Transcript [Zontivity] 2014*). Subgroup analyses have concluded that increased bleeding risks may not be observed in all populations. A pre-specified subgroup analysis of stable patients with a history of previous MI determined that Zontivity reduced the primary endpoint, whether treated concomitantly with a thienopyridine or not, and the risks of GUSTO moderate or severe bleeding were similarly increased irrespective of thienopyridine use (P-interaction = 0.37) (*Bohula et al 2015*). Other subgroup analyses have been published and include a number of the TRA 2°P–TIMI 50 primary study authors. These subgroup analyses found a significant difference in the composite primary endpoint of CV death, MI, or stroke for patients with a prior MI but no statistically significant difference in PAD patients; treatment with Zontivity in patients with a prior MI was also associated with greater reductions in CV death, MI, or stroke in patients with ≥ 1 risk factors for recurrent events, with greatest risk reductions in patients with ≥ 3 risk factors (*Bohula et al 2016, Bonaca et al 2013, Scirica et al 2013*). However, the quality of the sub-group analyses is not superior to that of the primary study and the validity of the results is uncertain as methodological limitations were noted. A MA of 5 RCTs (N = 40,630) demonstrated treatment with Zontivity vs placebo resulted in a statistically non-significant reduction in risk of MI (risk reduction [RR] 0.86; 95% CI, 0.80 to 0.93; p = 0.427) and ischemic stroke (RR, 0.84; 95% CI, 0.72 to 0.97; p = 0.92), with no observed differences in all-cause mortality or TIMI bleeding (*Sharma et al 2017*).
- The FDA approval of Yosprala (ASA DR/omeprazole) was based on 2 identically-designed, 6-month, phase 3, MC, DB, active-control (AC), RCTs conducted in the U.S. The trials compared Yosprala 325/40 mg (n = 524) to enteric-coated (EC) ASA 325 mg (n = 525), each administered orally once daily for secondary CV disease prevention in patients who had been taking ASA 325 mg daily for ≥ 3 months and who were at risk for ASA-associated gastric ulcers. Patients taking non-ASA non-steroidal anti-inflammatory drugs (NSAIDs) at baseline were allowed to continue therapy if use was chronic and expected to continue throughout the study period. The primary endpoint was the cumulative incidence of endoscopically-determined gastric ulceration over 6 months. Yosprala significantly reduced the cumulative incidence of gastric ulcers vs EC ASA 325 mg in the pooled analysis (3.2 vs 8.6%, respectively; p < 0.001). Among NSAID-users at baseline, the cumulative incidence of endoscopic gastric ulcer at month 6 was 4.5% with Yosprala vs 10.2% in the EC ASA group, while rates among patients not taking NSAIDs were 3.1% with Yosprala vs 8.4% in the EC ASA group.

Significantly fewer patients treated with Yosprala discontinued therapy due to pre-specified upper GI AEs vs patients treated with EC ASA arm (1.5 vs 8.2%, respectively; p < 0.001) (*Whellan et al 2014*).

- The long-term CV and GI safety of Yosprala were evaluated in a 12-month, phase 3, MC, open-label, single-arm trial among patients who were taking ASA 325 mg daily for ≥ 3 months for secondary CVD prevention and were at risk for ASA-associated upper GI events (n = 379). After 12 months, no new or unexpected safety events were noted with Yosprala, while the most common treatment-emergent GI AEs were diarrhea, dyspepsia, and nausea (each occurred in 4 to 5% of the overall safety population). Gastroesophageal reflux disease (GERD) was reported in 1.8% of the overall population (*Goldstein et al 2016*).
- Durlaza 162.5 mg was the first ASA ER formulation approved by the FDA to reduce the risk of death and MI in patients with chronic CAD, and to reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or TIA. New efficacy studies were not submitted to the FDA for the approval of Durlaza. While Durlaza 162.5 mg has a similar pharmacodynamic effect as immediate-release ASA 81 mg, the clinical benefits of the ER formulation vs immediate-release formulations of ASA are not yet known (*Drugs@FDA.gov 2020*).
- There is no evidence to support the use of dipyridamole in the acute treatment of patients presenting with a non-ST-segment elevation ACS (*Harrington 2008*). In addition, the results of a large MA of 29 RCTs demonstrated that in patients with arterial vascular disease, dipyridamole had no clear effect on the secondary prevention of vascular death. Compared to control (no drug or another antiplatelet inhibitor), dipyridamole appeared to reduce the risk of vascular events; however, the effect was only significant in patients presenting with cerebral ischemia (*De Schryver et al 2007*).
- In patients with stable intermittent claudication, cilostazol therapy has been shown to provide improvement in walking distance and speed as determined by standardized exercise treadmill tests and functional status questionnaires (*Beebe et al 1999, Bedenis et al 2014, Money et al 1998, Reilly 2001*). Results of several randomized, DB, PC studies of 6 to 24 weeks' duration indicate that cilostazol is more effective than placebo in increasing initial (until onset of claudication pain) and absolute (intolerable pain) claudication distances (*Bedenis et al 2014, Beebe et al 1999, Money et al 1998, O'Donnell et al 2009a, O'Donnell et al 2009b, Reilly 2001*). Limited data suggest that cilostazol (100 mg twice daily) also may be more effective than pentoxifylline (400 mg 3 times daily) in improving walking distance in patients with intermittent claudication (*Bedenis et al 2014, Beebe et al 1999, Dawson et al 2000, Hiatt 2001, Reilly 2001*).
- Because of its antiplatelet activity, cilostazol has been used alone or in combination with other antiplatelet agents (eg, ASA, Plavix) to prevent thrombosis and restenosis following coronary angioplasty/stent implantation (*Douglas et al 2005, Guyatt et al 2012, Kunishima et al 1997, Park et al 1999, Park et al 2000, Schömig et al 2005, Take et al 1997, Tsuchikane et al 1999, Xu et al 2016, Yoon et al 1999, Zou et al 2015*). In a randomized, DB, PC study, patients undergoing coronary artery stent implantation with bare-metal stents who received cilostazol (100 mg twice daily for 6 months) in addition to therapy with ASA and Plavix (75 mg daily for 30 days) had a larger minimal coronary artery lumen diameter (primary end point) and a 36% reduction in the risk of restenosis (defined as narrowing of the stented coronary artery lumen by at least 50% as documented by quantitative coronary angiography) (*Douglas et al 2005, Schömig et al 2005*). However, more studies, including a RCT and a SR of 10 RCTs, comparing triple antiplatelet therapy (ASA, Plavix, and cilostazol) with DAPT (ASA and Plavix), failed to demonstrate or exclude a beneficial effect of cilostazol on clinical outcomes (eg, reinfarction, major bleeding, mortality, periprocedural MI) when added to Plavix and ASA therapy (*Guyatt et al 2012, Xu et al 2016*). For patients undergoing DES implantation in coronary arteries, a MA of 7 RCTs evaluated the long-term efficacy and safety of adding cilostazol to conventional DAPT (ASA and Plavix). The analysis demonstrated that the addition of cilostazol was associated with a significant reduction in MACE vs DAPT (RR, 0.66; 95% CI, 0.50 to 0.88), without increasing bleeding, but was associated with significantly higher rates of rash, GI adverse effects, headache, and drug discontinuation (*Zou et al 2015*).
- Agrylin is the only platelet inhibitor to be FDA-approved for the treatment of thrombocythemia associated with myeloproliferative disorders, and the agent has demonstrated safety and efficacy for this indication (*Anagrelide study group 1992, Birgegard et al 2004, Dombi et al 2017, Harrison et al 2005, Penninga et al 2004, Silver 2005, Steurer et al 2004, Wiviott et al 2007*).

CLINICAL GUIDELINES

- Antiplatelet therapy is recommended for a variety of indications. The selection of $P2Y_{12}$ inhibitor therapy for patients with CAD varies greatly by individual patient characteristics and bleeding risks. All guidelines agree and recommend long-term treatment with ASA, or Plavix for those who cannot tolerate ASA in patients with ACS (*Amsterdam et al 2014, Guyatt et al 2012, Ibanez et al 2018, January et al 2014, January et al 2019, Levine et al 2011, Levine et al 2016a, Levine et al 2016b, Lip et al 2018, O'Gara et al 2013, Piepoli et al 2016*).

- The 2016 American College of Cardiology (ACC)/AHA guidelines for DAPT in patients with CAD have updated duration recommendations for 6 previously published guidelines based on data around newer generation stents. Recommendations vary based on the benefit/risk profiles of CAD patients but overall, minimum courses of DAPT therapy are now recommended in certain patients. Newer key recommendations include: (1) Plavix therapy for a minimum of 6 months for patients treated with DES; (2) any $P2Y_{12}$ inhibitor treatment for 12 months in those with ACS; (3) extended DAPT continuation in patients who have low bleeding risk; and (4) shorter duration of DAPT for patients at lower ischemic risk with high bleeding risk and longer DAPT periods for patients at elevated ischemic risk with lower bleeding risk (*Levine et al 2016a*). In 2017, the European Society of Cardiology (ESC) also published guidelines for DAPT in patients with CAD. Recommendations are largely consistent with the 2016 ACC/AHA guidelines for DAPT with several additions. In patients with CAD treated with coronary stent implantation, Plavix plus ASA is recommended for 6 months, irrespective of stent type. In patients with CAD treated with bioresorbable vascular scaffolds, DAPT should be considered for at least 12 months. Brilinta plus ASA is recommended for patients with ACS who do not have contraindications to the drug. For patients with NSTEMI undergoing PCI who are $P2Y_{12}$ inhibitor-naïve, or those with STEMI initially managed with conservative strategies, but now requiring a PCI, Effient plus ASA is recommended unless contraindications exist (*Valgimigli et al 2018*).
- The 2016 ESC guidelines updated recommendations on CV disease prevention. Key recommendations include: (1) in patients with ACS, DAPT with a $P2Y_{12}$ inhibitor (no agent recommended over another) and ASA for 12 months is recommended, unless there are contraindications (e.g., excessive risk of bleeding); (2) a shorter duration of $P2Y_{12}$ inhibitor administration (ranging from 3 to 6 months) should be considered for patients with higher bleed risks after DES implantation; (3) in non-cardioembolic ischemic stroke or TIA, prevention with ASA only, or Aggrenox or Plavix alone is recommended; and (4) in patients with stable CAD, Effient is not recommended and Brilinta is not recommended in stable CAD without a prior ACS (*Piepoli et al 2016*). Many of these recommendations are echoed in the 2017 ESC guidelines for DAPT (*Valgimigli et al 2018*). Additionally, the 2017 guidelines note that continuation of DAPT with Plavix for 6 to 30 months may be considered for patients with stable CAD who have tolerated therapy without complications but continue to have a high thrombotic risk. One month of DAPT can also be considered for patients with stable CAD in whom a 3-month DAPT poses safety concerns. The 2019 ESC guidelines for chronic coronary syndromes recommend DAPT with Plavix and ASA for 6 months following coronary stenting (assuming a normal risk of bleeding); duration of DAPT may be shortened to 3 months or 1 month, depending on risk of bleeding (*Knuuti et al 2020*). ASA monotherapy is recommended for patients with chronic coronary syndromes and previous MI or revascularization, but Plavix may be used as an alternative, particularly for patients with ASA intolerance or history of PAD or stroke/TIA. Adding another antithrombotic drug (no preferred agent) to ASA for long-term prevention may be considered in patients who have a moderate or high risk of ischemic events and no high bleeding risk.
- Other guidelines come from the American College of Chest Physicians (ACCP), which recommend Plavix plus ASA for 6 to 12 months in patients undergoing PCI and stent placement. Effient should not be used in patients < 60 kg, > 75 years of age or with a prior history of stroke. In patients who are stopping anticoagulant therapy and do not have a contraindication to ASA, it is recommended to administer ASA over no ASA to prevent recurrent venous thromboembolism (*Guyatt et al 2012, Kearon et al 2016*).
- The AHA/ACC, 2020 ESC guidelines for the management of patients with NSTEMI ACS, and 2017 ESC guidelines for DAPT provide more specific $P2Y_{12}$ inhibitor recommendations compared to other reputable society groups. For those patients with moderate to severe risk of ischemic events, DAPT with ASA is recommended; however, Brilinta is specifically recommended over Plavix for up to 12 months of treatment. From the 2020 ESC updates for the treatment of NSTEMI ACS, Effient may be considered preferred over Brilinta in patient with NSTEMI-ASC patients who proceed to PCI. A switch from Effient or Brilinta to Plavix may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition. According to the 2015 ESC guidelines, Zontivity may be added to ASA and Plavix for patients with a history of MI, but efficacy is modest and must be weighed against the risk for bleeds. Routine pre-treatment with a $P2Y_{12}$ inhibitor in patients in whom coronary anatomy is not known and early invasive therapy is planned (*Amsterdam et al 2014, Collet et al 2020, January et al 2014, January et al 2019, O'Gara et al 2013, Valgimigli et al 2018*).
- According to the 2019 AHA/ACC focused update for the management of atrial fibrillation (AF), if triple therapy (oral anticoagulant, ASA, and $P2Y_{12}$ inhibitor) is prescribed in AF patients at increased risk of stroke and have undergone PCI, it is reasonable to choose Plavix over Effient. Double therapy with a $P2Y_{12}$ inhibitor (Plavix or Brilinta) and dose-adjusted warfarin or double therapy with a $P2Y_{12}$ inhibitor (Plavix) and certain oral anticoagulants (eg, low dose rivaroxaban 15 mg once daily or dabigatran 150 mg twice daily) are reasonable to reduce the risk of bleeding compared

to triple therapy. The 2018 ACCP guidelines for antithrombotic therapy for patients with AF recommend antiplatelet agents (preferably Plavix) for patients with AF undergoing PCI/stenting; the use and duration of triple therapy (2 antiplatelet agents plus an oral anticoagulant) and dual therapy (single antiplatelet agent plus an oral anticoagulant) is dependent on the risk of bleeding and thrombosis (*January et al 2014, January et al 2019, Lip et al 2018*).

- The 2017 ESC guidelines for the management of patients with a STEMI provide the following recommendations for the periprocedural use of platelet aggregation inhibitors in patients undergoing primary PCI: (1) unless there are contraindications such as excessive risk of bleeding, Effient or Brilinta (or Plavix if these are not available or are contraindicated), is recommended before (or at latest at the time of) PCI and should be continued for 12 months; (2) ASA should be administered as soon as possible for patients without contraindications. For patients undergoing fibrinolytic therapy, Plavix plus ASA is recommended. However, patients who undergo PCI should be switched to Effient or Brilinta 48 hours after fibrinolysis. DAPT (ASA plus a $P2Y_{12}$ inhibitor) is recommended for up to 1 year in patients undergoing fibrinolysis plus PCI (*Ibanez et al 2018*). According to the 2017 ESC guidelines for DAPT, pre-treatment with Plavix may be warranted for patients with stable CAD who have a high probability of PCI (*Valgimigli et al 2018*).
- The 2011 AHA/American College of Cardiology Foundation (ACCF) guidelines for secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease recommends ASA, or Plavix if ASA is not tolerated, in all patients with CAD. A $P2Y_{12}$ inhibitor in combination with ASA is recommended in patients after ACS or PCI with stent placement, while patients receiving a bare-metal stent or DES during PCI for ACS should be given Plavix, Effient, or Brilinta for at least 12 months. Patients undergoing coronary artery bypass grafting should be given ASA for 1 year after surgery (*Smith et al 2011*). According to the 2017 ESC guidelines for DAPT, Brilinta or Effient plus ASA may be considered instead of Plavix in stable CAD patients undergoing PCI, taking into account ischemic and bleeding risks (*Valgimigli et al 2018*). These guidelines also recommend Plavix plus ASA in stable CAD patients undergoing coronary stent implantation and in ACS patients who cannot receive Brilinta or Effient, including those with prior intracranial bleeding or an indication for oral anticoagulation.
- According to the 2017 ESC guidelines for DAPT, a proton pump inhibitor (PPI) in combination with DAPT is recommended to minimize bleeding (*Valgimigli et al 2018).*
- The 2012 ACCP guidelines have included recommendations for ASA monotherapy or Aggrenox twice daily for initial therapy for TIA or ischemic stroke in order to prevent stroke (*Guyatt et al 2012*). The AHA/American Stroke Association (ASA) guidelines for acute ischemic stroke reinforce that the combination of ASA and Plavix might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 90 days (*Kernan et al 2014, Powers et al 2018*). A 2019 update to the AHA/ASA guidelines for early management of acute stroke recommends that ASA be started within 24 to 48 hours after stroke onset; in patients with minor noncardioembolic strokes who did not receive alteplase, dual therapy with ASA and Plavix has been shown to reduce recurrent ischemic stroke if initiated within 24 hours of symptom onset and continued for 21 days (*Powers et al 2019*). Other guidelines state Plavix plus ASA is probably more effective at reducing stroke compared with ASA monotherapy, but is less effective than warfarin (*Culebras et al 2014, Kernan et al 2014*). The 2014 AHA/ASA guidelines for the primary prevention of stroke state that current clinical data reflect risk but no benefit of ASA for the prevention of a first stroke in the general population, and that there is no evidence that antiplatelet medications reduce the risk of stroke in the general population at low risk (*Meschia et al 2014*). A 2017 AHA/ASA statement on the prevention of stroke in patients with silent cerebrovascular disease recommends that it is reasonable to avoid antiplatelet agents when there is no specific CV or cerebrovascular indication, but to otherwise use them according to currently recommended indications (*Smith et al 2017*). The 2011 AHA/ACCF guidelines recommend that patients with extracranial carotid or vertebral atherosclerosis who have had ischemic stroke or TIA should be given ASA alone, Plavix alone, or a combination of Aggrenox (*Smith et al 2011*). The 2018 AHA/ASA guidelines for acute ischemic stroke note that Brilinta is not recommended over ASA in the treatment of minor stroke; this recommendation is echoed in the 2019 update (*Powers et al 2018, Powers et al 2019*).
- For the treatment of PAD, treatment with ASA is recommended for asymptomatic disease, and ASA or Plavix is recommended for secondary prevention of CV events in symptomatic PAD but not as dual therapy (*Alonso-Coello et al 2012, Smith et al 2011*). However, the 2011 ACC/AHA guidelines do state the combination of ASA and Plavix may be considered to reduce the risk of CV events in patients with symptomatic PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity (*Anderson et al 2013*). The 2016 ACC/AHA guidelines for patients with lower extremity PAD recommend antiplatelet therapy with ASA alone (75 to 325 mg per day) or Plavix alone (75 mg per day) to reduce MI, stroke, and vascular death in patients with symptomatic PAD (*Gerhard-Herman et al 2016*). The 2017 ESC guidelines for patients with PAD also recommend single-agent antiplatelet therapy (Plavix is preferred over ASA) for symptomatic patients, but recommend ASA plus Plavix for at least 1 month after coronary artery

stenosis. Other indications for DAPT in the setting of PAD include after infra-inguinal stent implantation for at least 1 month, and in below-the-knee bypass with a prosthetic graft. Antiplatelet therapy is not routinely recommended for patients with isolated asymptomatic lower extremity arterial disease (*Aboyans et al 2018*).

- The 2012 ACCP guidelines recommend the addition of cilostazol to ASA or Plavix therapy in patients with refractory intermittent claudication who do not respond to conservative measures (*Guyatt et al 2012, Alonso-Coello et al 2012*). The 2016 ACC/AHA guidelines for patients with lower extremity PAD recommend cilostazol as an effective therapy to improve symptoms and increase walking distance in patients with claudication (*Gerhard-Herman et al 2016*). The 2017 ESC guidelines for patients with PAD do not specifically recommend cilostazol for patients with intermittent claudication, but do acknowledge that this agent may yield mild-to-moderate improvements in walking distance (*Aboyans et al 2018*).
- The 2017 AHA/ACC guidelines for the management of patients with valvular heart disease recommend antithrombotic therapy with ASA in addition to anticoagulation with a vitamin K antagonist in patients with a mechanical valve prosthesis, and daily ASA in all patients with a bioprosthetic aortic or mitral valve. Compared with oral anticoagulation alone, the addition of DAPT increases bleeding complications by at least 2- to 3-fold. Plavix 75 mg daily may be a reasonable antithrombotic therapy option for the first 6 months after transcatheter aortic valve replacement (TAVR), in addition to life-long ASA 75 mg to 100 mg daily (*Nishimura et al 2017*). The 2017 ESC guidelines for the management of valvular heart disease provide the following recommendations for patients with mechanical prosthesis: (1) triple therapy with ASA, Plavix, and a vitamin K antagonist for at least 1 month for patients treated with coronary stent implantation, irrespective of type of stent used; (2) triple therapy for 1 to 6 months is recommended for those with high ischemic risk due to ACS or other characteristics, when the benefits of therapy outweigh the bleeding risk; (3) dual therapy with a vitamin K antagonist and Plavix should be considered for patients in whom the bleeding risk outweighs the ischemic risk. The following are recommendations for patients with bioprostheses: (1) dual antiplatelet therapy should be considered for the first 3 to 6 months after transcatheter aortic valve implantation, followed by lifelong single antiplatelet therapy (in patients who do not need oral anticoagulation for other reasons); (2) antiplatelet therapy with a single agent can be considered after transcatheter aortic valve implantation for patients with a high risk of bleeding) (*Baumgartner et al 2018*).
- The updated 2019 Beers Criteria published by the American Geriatric Society (AGS) recommends avoiding short-acting dipyridamole and cilostazol in elderly patients, and recommends cautious use of ASA and Effient in older adults (*AGS 2019*). The criteria also recommends against scheduled use of proton-pump inhibitors, such as omeprazole, for more than 8 weeks unless they are used for high-risk patients.

SAFETY SUMMARY

- Boxed warnings associated with antiplatelet treatment include significant, sometimes fatal, bleeding with Brilinta, Effient, and Zontivity treatment. Additionally, Effient should not be prescribed in patients ≥ 75 years of age, body weight < 60 kg, those with a propensity to bleed, and with concomitant use of medications that increase the risk of bleeding. Brilinta should not be used with ASA in doses > 100 mg due to reduced effectiveness. The effectiveness of Plavix is dependent on the activation of CYP2C19; therefore, there is a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene (termed “CYP2C19 poor metabolizers”). The use of another platelet $P2Y_{12}$ inhibitor should be considered in patients identified as CYP2C19 poor metabolizers. Additionally, Plavix has a warning and precaution for diminished antiplatelet activity with concomitant use of drugs that interfere with CYP2C19 (e.g., omeprazole, esomeprazole). Concomitant use with omeprazole or esomeprazole and Plavix should be avoided. Cilostazol is contraindicated in patients with heart failure of any severity.
- Plavix, Effient, Brilinta, and Zontivity are contraindicated in patients with active pathological bleeding such as bleeding peptic ulcer or ICH, and active pathologic bleeding is cited as a warning and precaution within the cilostazol labeling. Withholding Zontivity for a brief period will not be useful in managing an acute bleeding event because of its long half-life. There is no known treatment to reverse the antiplatelet effect of Zontivity, and significant inhibition of platelet aggregation remains 4 weeks after discontinuation. Because of the short half-life of Plavix’s active metabolite, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective.
- Effient and Zontivity are also contraindicated in patients with a history of prior TIA or stroke, and Brilinta and Zontivity are contraindicated in patients with a history of ICH. Aggrenox, Durlaza, and Yosprala are contraindicated in patients with a known allergy to NSAIDs, in patients with asthma, rhinitis, and nasal polyps, or in children or adolescents with viral infections due to the risk of Reye’s syndrome. Other contraindications are included within boxed warnings.
- Agrylin has no contraindications.

- Plavix, Brilinta, and Effient should be discontinued prior to surgery. Thrombotic thrombocytopenic purpura (TTP) may occur after brief exposure (< 2 weeks) of Plavix, Brilinta, or Effient. Premature discontinuation of Plavix, Brilinta, or Effient may increase the risk of CV events. Dyspnea has been reported in patients administered Brilinta; continuation with Brilinta without interruption or another antiplatelet should be considered. Brilinta can cause ventricular pauses, bradyarrhythmias including AV block. Brilinta has not been studied in patients with severe hepatic impairment. The concentrations of Brilinta and its metabolite and platelet inhibition are expected to be similar in patients with end-stage renal disease on intermittent hemodialysis vs patients with normal renal function. In patients with severe hepatic impairment, concentrations of Brilinta are likely to be increased. Brilinta may cause false negative platelet functional test results in patients with heparin-induced thrombocytopenia. Hypersensitivity reactions, including rash and angioedema, have been reported with Plavix and Effient use in patients with a history of prior thienopyridine hypersensitivity.
- Aggrenox, Durlaza, and Yosprala should be used with caution in patients at increased bleeding risk such as patients with GI ulcers, a history of active peptic ulcer disease, and/or concomitant alcohol (≥ 3 drinks daily). Agents containing ASA may cause fetal harm, especially during the third trimester. ASA and Agrylin should not be co-administered as use increases the risk of bleeding.
- Concomitant use of Yosprala with Plavix should be avoided, as omeprazole reduces the pharmacologic activity of Plavix. Omeprazole has also been associated with acute interstitial nephritis, *Clostridium difficile*-associated diarrhea, increased risk of bone fracture, cutaneous and systemic lupus erythematosus, hypomagnesemia, and vitamin B-12 deficiency. Concomitant Yosprala and PPI use is associated with an increased risk of fundic gland polyps that increase with long-term use, especially beyond 1 year.
- Agrylin may cause vasodilation, tachycardia, palpitations, pulmonary hypertension, and congestive heart failure (CHF). Other drugs that inhibit PDE-3 have caused decreased survival when compared with placebo in patients with CHF (Class III to IV). Because of the positive inotropic effects and side effects of Agrylin, a pre-treatment CV examination is recommended in addition to careful monitoring during treatment. Agrylin increased QT prolongation in healthy volunteers; therefore, Agrylin should not be used in patients with known risk factors for QT prolongation. In addition, interstitial lung diseases, mostly as progressive dyspnea with lung infiltrations, have been reported to be associated with the use of Agrylin in postmarketing reports.
- Cilostazol may induce tachycardia, palpitation, tachyarrhythmia or hypotension, with an associated increase in heart rate of approximately 5 to 7 bpm. Increased risks of exacerbations of angina pectoris or MI may occur in patients with a history of ischemic heart disease. Left ventricular outflow tract obstruction has been reported in patients with sigmoid shaped interventricular septum after starting cilostazol. Patients should be monitored for the development of a new systolic murmur or cardiac symptoms. Cilostazol has not been studied in patients with hemostatic disorders or active bleeding and should be avoided in these groups. Patients should be monitored periodically for complete blood count (CBC) abnormalities. Cilostazol has not been studied in patients with moderate or severe hepatic impairment.
- Dipyridamole has a vasodilatory effect and should be used with caution in patients with severe CAD or in patients with hypotension. Chest pain may be aggravated in patients with underlying CAD who are receiving dipyridamole. Elevations of hepatic enzymes and hepatic failure have been reported in association with dipyridamole administration.
- Patients undergoing pharmacological stress testing with adenosinergic agents should not take Aggrenox or dipyridamole within 48 hours prior to stress testing.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Agrylin (anagrelide)	Capsules	Oral	Pediatric: Once daily Adult: 2 to 4 times daily	Adjust to the lowest effective dosage required to reduce and maintain platelet count < 600,000/µL in adults. Avoid with severe hepatic impairment.
Durlaza (ASA ER)	Capsules	Oral	Once daily	Do not take 2 hours before or 1 hour after consuming alcohol.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Take with a full glass of water at the same time each day. Swallow whole. Do not cut, crush, or chew capsules. Avoid with severe renal or hepatic impairment.
cilostazol	Tablets	Oral	Twice daily	Reduce dose with concomitant CYP3A4 or CYP2C19 inhibitors. Take at least half an hour before or 2 hours after breakfast and dinner. If symptoms are not improved after 3 months, discontinue treatment. Moderate or severe hepatic impairment have not been studied.
Plavix (clopidogrel)	Tablets	Oral	Once daily†	--
dipyridamole	Tablets, IV solution	Oral, IV	Tablets: Four times daily‡	--
Effient (prasugrel)	Tablets	Oral	Once daily§‖	Take with or without food. Consider a lower dose for patients < 60 kg. Patients should also take ASA daily. Not studied in severe hepatic impairment, generally at higher risk of bleeding.
Brilinta (ticagrelor)	Tablets	Oral	Twice daily	Take with or without food. Administer with ASA. May be crushed, mixed with water, and drunk or administered via nasogastric tube. Avoid with severe hepatic impairment.
Zontivity* (vorapaxar)	Tablets	Oral	Once daily	Take with or without food. Use with ASA and/or Plavix according to their indications or standard of care. There is limited experience with other antiplatelets and none with Zontivity as the only antiplatelet agent. Avoid with severe hepatic impairment.
Aggrenox (ASA/ ER dipyridamole)	Capsules	Oral	Twice daily	Take with or without food. Do not chew capsule.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				In case of intolerable headaches during initial treatment, switch to 1 capsule at bedtime and low-dose ASA in the morning; resume twice daily dosing within 1 week. Avoid with severe renal and hepatic impairment.
Yosprala (ASA DR/omeprazole)	Tablets	Oral	Once daily	Take at least 60 minutes before a meal. Swallow whole with liquid. Do not split, chew, crush, or dissolve the tablet. Avoid with severe renal impairment and any degree of hepatic impairment.

See the current prescribing information for full details
*There is limited clinical experience with other antiplatelet drugs or with Zontivity as a monotherapy agent. Also due to the risk of bleeding, Zontivity should be avoided in patients taking warfarin or other anticoagulants. Withholding Zontivity for a brief period will not be useful in managing acute bleeding events because of its long half-life. Significant inhibition of platelet aggregation remains 4 weeks after discontinuation.
† Initiating Plavix without a loading dose will delay establishment of an antiplatelet effect by several days for certain indications.
‡ As adjunct to the usual warfarin therapy. ASA is not to be administered concomitantly with coumarin anticoagulants.
§ In the clinical trial, the loading dose of Effient was not administered until coronary anatomy was established in UA/NSTEMI patients and in STEMI patients presenting >12 hours after symptom onset. In STEMI patients presenting within 12 hours of symptom onset, the loading dose was administered at the time of diagnosis, although most received Effient at the time of PCI. For the small fraction of patients that required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial.
‖ The safety and efficacy of the 5 mg dose have not been prospectively studied.

CONCLUSION

- The platelet inhibitors play an important role in the treatment and prevention of cerebrovascular and CV diseases.
- Antiplatelet agents have different sites of action. ASA is a COX-1 inhibitor. Plavix and Effient irreversibly block $P2Y_{12}$, a key adenosine phosphate receptor on the platelet surface. Brilinta is a reversible inhibitor of $P2Y_{12}$. Zontivity is a first-in-class selective antagonist of the PAR-1, which is a receptor on thrombin. The mechanism of action of dipyridamole, Agrylin, and cilostazol are not completely understood, but each is believed to inhibit platelet aggregation. Plavix has incomplete platelet inhibition, a slower onset of action, and poor response in some patients.
- Plavix has been shown to significantly reduce the odds of a serious vascular event in high-risk patients. Study data has demonstrated that Plavix significantly reduced the risk of stroke, MI, and vascular death compared to ASA in patients with a recent ischemic stroke, MI, or established peripheral vascular disease. On the basis of the CURE, COMMIT, and CLARITY studies, Plavix received an FDA-approved indication for the reduction of atherothrombotic events in patients with ACS and MI, and Plavix has been incorporated into the current treatment guidelines for the management of these conditions (*Amsterdam et al 2014, Collet et al 2020, COMMIT 2005, Culebras et al 2014, CURE 2001, Gerhard-Herman et al 2016, Ibanez et al 2018, January et al 2014, January et al 2019, Lip et al 2018, O'Gara et al 2013, Sabatine et al 2005a, Sabatine et al 2005b, Valgimigli et al 2018*).
- Plavix's effectiveness is dependent on its conversion to its active metabolite mostly by CYP2C19. Patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel, diminished antiplatelet responses, and generally exhibit higher CV event rates following MI than patients with normal CYP2C19 function. In addition, concomitant use of Plavix with proton pump inhibitors, particularly those extensively inhibiting CYP2C19, may also increase CV events.
- Effient may be the most potent of these agents, with more desirable characteristics compared to Plavix with regard to drug-drug interactions and interpatient enzyme variability (*Serebruany et al 2009, Wiviott et al 2007*). Initial FDA-approval of Effient was based on the results from the TRITON-TIMI 38 study, which compared Plavix to Effient. Effient has demonstrated efficacy in reducing ischemic events in patients with ACS who underwent PCI. Although compared to Plavix, there were no differences in the important outcomes of all-cause and CV mortality, and Effient demonstrated more major bleeding. The overall recommendation is for a thienopyridine to be used in ACS patients who are managed with PCI, with Plavix, Effient, and Brilinta listed as potential options. Of note, the use of Effient in STEMI patients with a

prior history of stroke or TIA for which primary PCI is planned is not recommended (*Levine et al 2011, Levine et al 2016b*).

- Brilinta is FDA-approved to reduce the rate of thrombotic CV events in patients with ACS, including UA, NSTEMI, and STEMI and to reduce the risk of a first MI or stroke in patients with CAD at high risk for such events. Brilinta works in a similar manner to the other thienopyridine platelet inhibitors (Plavix and Effient). Brilinta is not a prodrug; therefore, it is not subject to potential drug interactions associated with the other agents (*Micromedex 2020*). PLATO was a pivotal clinical study establishing the safety and efficacy of Brilinta in reducing the rate of thrombotic CV events in patients with ACS, which compared Brilinta and Plavix in hospitalized patients with documented ACS, with or without ST-segment elevation. After 12 months of treatment, there was no difference in major bleeding; however, Brilinta significantly reduced all-cause and CV mortality. This efficacy benefit was not observed in North American patients (*Mahaffey et al 2011, Wallentin et al 2009*). The PEGASUS TIMI-54 trial reinforced benefit in patients with a history of MI in which a reduction in the rate of CV death, MI, and stroke was observed in patients treated with Brilinta 60 mg twice daily plus ASA over ASA monotherapy. The rates of CV mortality or all-cause mortality alone were not significantly different between groups, and increased risk of major bleeding was observed with Brilinta treatment (*Bonaca et al 2015*).
- Zontivity is FDA-approved for use in patients with a history of MI or PAD. Zontivity should be prescribed with ASA and/or Plavix according to their indications or standard of care, and not be used as monotherapy or concomitantly with warfarin or other anticoagulants. There is limited clinical experience with other antiplatelet drugs or with Zontivity as a monotherapy agent. Increased hemorrhagic stroke and bleeding rates in patients with a history of stroke or TIA caused the Zontivity phase 3 studies to be terminated early. In the TRA2°P-TIMI 50 trial, Zontivity demonstrated lower rates of the composite of CV mortality, MI, or stroke vs placebo when added to standard antiplatelet therapy for secondary prevention of CV events in PAD or MI who have not undergone PCI. Significance was driven by MI reductions (*Morrow et al 2012, Tricoci et al 2012, FDA Summary Review [Zontivity] 2014, FDA Advisory Committee Transcript [Zontivity] 2014*).
  - When managing acute bleeding events, withholding Zontivity may not be helpful because of its long half-life. Significant inhibition of platelet aggregation remains 4 weeks after discontinuation. Also, the optimal time for initiation and duration of Zontivity therapy remain poorly defined (*FDA Summary Review [Zontivity] 2014, Morrow et al 2012, Tricoci et al 2012*).
  - The 2016 ESC guidelines for CV disease prevention stipulate that Zontivity cannot be recommended systematically in patients with stable atherosclerotic disease; however, the 2015 ESC guidelines state Zontivity may be added to ASA and Plavix for patients with a history of MI. The ESC acknowledges that efficacy is modest and must be weighed against the risk for bleeds (*Piepoli et al 2016*).
- Dipyridamole has been shown to reduce stroke recurrence in patients with previous ischemic cerebrovascular disease compared to placebo but has not been shown to be more effective than ASA (*Diener et al 1996, Leonardi-Bee et al 2005*). Aggrenox significantly reduced the risk of stroke by 37% compared to 18% with ASA and 16% with ER dipyridamole. There was no significant difference in all-cause mortality among the active treatment groups (*Diener et al 1996*). Aggrenox significantly reduced the composite of death, nonfatal stroke or MI and major bleeding to 13% of patients compared to 16% for ASA monotherapy; however, the combination regimen was discontinued more often, mainly because of headache (*Halkes et al 2006*).
- Cilostazol is used for the symptomatic treatment of intermittent claudication and is recommended as an effective therapy to improve symptoms and increase walking distance in patients with claudication due to lower extremity PAD (*Gerhard-Herman et al 2016*). Long-term effects of the drug on limb preservation and hospitalization have not been fully elucidated. Studies and SRs have failed to demonstrate or exclude a beneficial effect of cilostazol on clinical outcomes when added to Plavix and ASA therapy. Currently, experts generally do not recommend the use of cilostazol for the prevention of postprocedural complications in patients undergoing coronary artery stent placement, with the possible exception of those with an allergy or intolerance to ASA or Plavix. In such cases, ACCP states that cilostazol may be used as a substitute for either ASA or Plavix as part of the DAPT regimen (*Alonso-Coello et al 2012, Guyatt et al 2012, Levine et al 2011, Levine et al 2016b*).
- Agrylin is the only platelet inhibitor to be FDA-approved for the treatment of thrombocythemia associated with myeloproliferative disorders, and the agent has demonstrated safety and efficacy for this indication (*Anagrelide study group 1992, Birgegard et al 2004, Dombi et al 2017, Harrison et al 2005, Penninga et al 2004, Silver 2005, Steurer et al 2004, Wiviott et al 2007*).
- ASA is the most frequently studied platelet inhibitor and is generally the reference drug to which other treatments are compared. ASA is the platelet inhibitor recommended as first-line in most treatment guidelines for general use, including

initial management of noncardioembolic stroke or TIA, ACS, and MI, and for primary and secondary prevention in patients with cerebrovascular, CV, and peripheral vascular diseases (*Aboyans et al 2018*, *Amsterdam et al 2014, Culebras et al 2014, Gagne et al 2013, Gerhard-Herman et al 2016, Guyatt et al 2012, Ibanez et al 2018, Lip et al 2018, January et al 2014, January et al 2019, Kernan et al 2014, Knuuti et al 2020, Kohli et al 2014, O'Gara et al 2013, Powers et al 2018, Powers et al 2019, Smith et al 2011, Smith et al 2017, Valgimigli et al 2018*). Evidence supporting the efficacy of ASA has demonstrated a reduction in vascular death of ~15% and in nonfatal vascular events of ~30% (*Eikelboom et al 2012*). In the US, nearly 40% of adults > 50 years of age use ASA for the primary or secondary prevention of CV disease (*Bibbins-Domingo et al 2016*).

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Publication Date: October 2, 2020

Prior Authorization Guideline

Guideline Name Xywav (calcium, magnesium, potassium, and sodium oxybates)

1 . Indications

Drug Name: Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution
Narcolepsy with Cataplexy (Narcolepsy Type 1) Indicated for the treatment of cataplexy in patients 7 years of age and older with narcolepsy. **Narcolepsy without Cataplexy (Narcolepsy Type 2)** Indicated for the treatment of excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

2 . Criteria

Product Name: Xywav	
Diagnosis	Narcolepsy with Cataplexy (Narcolepsy Type 1) [A]
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization
Approval Criteria **1** - Diagnosis of narcolepsy as confirmed by sleep study (unless the prescriber provides justification confirming that a sleep study would not be feasible)	

AND

2 - Symptoms of cataplexy are present

AND

3 - Symptoms of excessive daytime sleepiness (e.g., irrepressible need to sleep or daytime lapses into sleep) are present

AND

4 - Prescribed by or in consultation with one of the following:

- Neurologist
- Psychiatrist
- Sleep Medicine Specialist

Product Name: Xywav	
Diagnosis	Narcolepsy with Cataplexy (Narcolepsy Type 1)
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Documentation demonstrating a reduction in the frequency of cataplexy attacks associated with therapy

OR

2 - Documentation demonstrating a reduction in symptoms of excessive daytime sleepiness associated with therapy

Product Name: Xywav	
Diagnosis	Narcolepsy without Cataplexy (Narcolepsy Type 2) [B]
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of narcolepsy as confirmed by sleep study (unless the prescriber provides justification confirming that a sleep study would not be feasible)

AND

2 - Symptoms of cataplexy are absent

AND

3 - Symptoms of excessive daytime sleepiness (e.g., irrepressible need to sleep or daytime lapses into sleep) are present

AND

4 - Trial and failure, contraindication (e.g., safety concerns, not indicated for patient's age/weight), or intolerance to both of the following :

- generic modafinil or generic armodafinil
- Sunosi

AND

5 - One of the following:

5.1 Trial and failure, contraindication, or intolerance to an amphetamine (e.g., amphetamine, dextroamphetamine) or methylphenidate based stimulant

OR

5.2 History of or potential for a substance use disorder

AND

6 - Prescribed by or in consultation with one of the following:

- Neurologist
- Psychiatrist
- Sleep Medicine Specialist

Product Name: Xywav	
Diagnosis	Narcolepsy without Cataplexy (Narcolepsy Type 2)
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization
Approval Criteria **1** - Documentation demonstrating a reduction in symptoms of excessive daytime sleepiness associated with therapy	

3 . Endnotes

A. International classification of Sleep Disorders (ICSD-3) diagnostic criteria for narcolepsy with cataplexy (narcolepsy type 1) : 1. Daily periods of irrepressible need for sleep or daytime lapses into sleep (i.e., excessive daytime sleepiness) for at least 3 months. 2. Presence of one or both of the following: cataplexy and a mean sleep latency of less than or equal to 8 minutes and 2 or more sleep onset REM periods (SOREMPs) on a multiple sleep latency test (MSLT) performed using standard techniques (a SOREMP within 15 minutes of sleep onset on the preceding nocturnal polysomnogram may replace 1 of the SOREMPs on the MSLT); or cerebrospinal fluid (CSF) hypocretin-1 concentration is less than or equal to 110 pg/mL or less than one-third of the mean values obtained in normal subjects with the same standardized assay). 3. Exclusion of alternative causes of chronic daytime sleepiness by history, physical exam, and polysomnography. Other conditions that cause chronic daytime sleepiness include insufficient sleep, untreated sleep apnea, periodic limb movements of sleep, and idiopathic hypersomnia (chronic sleepiness but without SOREMPs or other evidence of abnormal REM sleep). In addition, the effects of sedating medications should be excluded. [2-4]

B. International classification of Sleep Disorders (ICSD-3) diagnostic criteria for narcolepsy without cataplexy (narcolepsy type 2) : 1. Daily periods of irrepressible need for sleep or daytime lapses into sleep (i.e., excessive daytime sleepiness) for at least 3 months. 2. Cataplexy is absent 3. CSF hypocretin-1 levels, if measured, is greater than 110 pg/mL or greater than one-third of the mean values obtained in normal subjects with the same standardized assay) 4. A mean sleep latency of less than or equal to 8 minutes and 2 or more sleep onset REM periods (SOREMPs) on a multiple sleep latency test (MSLT) performed using standard techniques (a SOREMP within 15 minutes of sleep onset on the preceding nocturnal polysomnogram may replace 1 of the SOREMPs on the MSLT). 5. Exclusion of alternative causes of chronic daytime sleepiness by history, physical exam, and polysomnography. Other conditions that cause chronic daytime sleepiness include insufficient sleep, untreated sleep apnea, periodic limb movements of sleep, and idiopathic hypersomnia (chronic sleepiness but without SOREMPs or other evidence of abnormal REM sleep). In addition, the effects of sedating medications should be excluded. [2-4]

4 . References

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2. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
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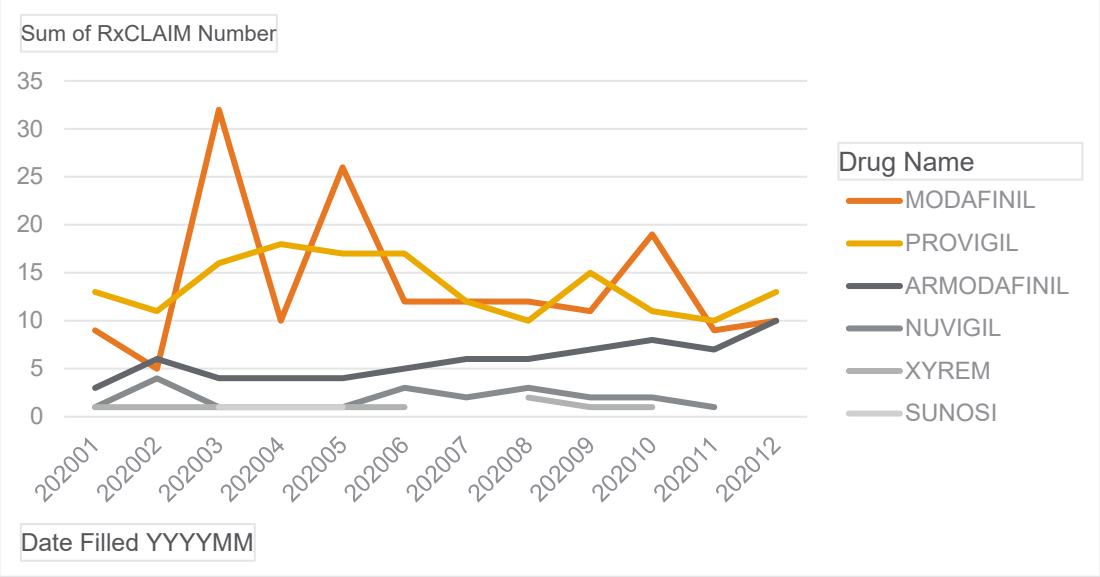
Nevada Medicaid

Narcolepsy Agents
Fee for Service
January 1, 2020 – December 31, 2020

Drug Name	Members	Count of Claims	Total Days Supply	Total Quantity
ARMODAFINIL	14	70	2,100	2,160
MODAFINIL	36	167	3,563	4,563
NUVIGIL	4	20	570	840
PROVIGIL	24	163	3,676	3,452
SUNOSI	1	5	150	150
XYREM	1	11	330	4,860



AAA. Narcolepsy Agents

Therapeutic Class: Narcolepsy Agents (non-stimulants)
Last Reviewed by the DUR Board: January 23, 2020

Narcolepsy Agents are subject to prior authorizations and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

a. Approval will be given if the following criteria are met and documented:

1. Provigil® (modafinil), and Nuvigil® (armodafinil):

a. The recipient has a diagnosis of narcolepsy.

2. Xyrem® (sodium oxybate):

a. The recipient has tried and failed on Provigil® (modafinil) or Nuvigil® (armodafinil); and/or

b. The recipient has a diagnosis of narcolepsy with cataplexy; and

c. The drug was prescribed by or in consultation with a neurologist or sleep specialist.

3. Prior Authorization Guidelines

a. Prior authorization approvals will be for one year.

b. Prior authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

b. Sunosi® (solriamfetol)

1. For treatment of Narcolepsy

a. Approval will be given if all the following criteria are met and documented:

1. The recipient has a diagnosis of narcolepsy confirmed by sleep study (unless the prescriber provides justification confirming that a sleep study would not be feasible); and

2. The recipient has had trial and failure, contraindication or intolerance to both of the following:

a. modafinil; and

b. armodafinil.

b. Recertification Request

1. Documentation of positive clinical response to Sunosi® therapy.

c. Prior Authorization Guidelines

1. Initial Authorization will be for 12 months.

2. Recertification approval will be for 12 months.

3. Prior authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

2. For treatment of Obstructive Sleep Apnea (OSA)

a. Approval will be given if all the following criteria are met and documented:

1. The recipient must have a diagnosis of OSA defined by one of the following:

a. The recipient has had 15 or more obstructive respiratory events per hour of sleep confirmed by a sleep study (unless the prescriber provides justification confirming that a sleep study would not be feasible); or

b. Both the following:

1. Five or more obstructive respiratory events per hour of sleep confirmed by a sleep study (unless the prescriber provides justification confirming that a sleep study would not be feasible); and

2. One of the following signs/symptoms are present:

a. Daytime sleepiness; or

b. Nonrestorative sleep; or

c. Fatigue; or

d. Insomnia; or

e. Waking up with breath holding, gasping, or choking; or

f. Habitual snoring noted by a bed partner or other observer; or

g. Observed apnea; and

2. Both the following:

a. The recipient has used a standard treatment(s) for the underlying obstruction for one month or longer (e.g. CPAP, BiPAP); and

b. The recipient is fully compliant with ongoing treatment(s) for the underlying airway obstruction; and

3. The recipient has had a trial and failure, contraindication or intolerance to both of the following:

a. Modafinil; and

b. Armodafinil.

b. Rectification Request (recipient must meet all the criteria):

1. Documentation of positive clinical response to Sunosi® therapy; and

2. The recipient continues to be fully compliant with ongoing treatment(s) for the underlying airway obstruction. (e.g. CPAP, BiPAP)

c. Prior Authorization Guidelines

1. Initial prior authorization approval is for six months.

2. Recertification approval is for six months.

3. Prior authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

MEDICATION*	MARKETER	AVAILABILITY
Nuvigil (armodafinil)	Teva Pharmaceuticals	**Brand/Generic:** 50, 150, 200, 250 mg tablets
Provigil (modafinil)	Teva Pharmaceuticals	**Brand/Generic:** 100, 200 mg tablets
Sunosi (solriamfetol)	Jazz Pharmaceuticals	**Brand:** 75, 150 mg tablets
Wakix (pitolisant)	Harmony Biosciences, LLC	**Brand:** 4.45, 17.8 mg tablets
Xyrem (sodium oxybate)	Jazz Pharmaceuticals	**Brand:** 500 mg/mL oral solution
Xywav (calcium, magnesium, potassium, and sodium oxybates)	Jazz Pharmaceuticals	**Brand:** 500 mg/mL oral solution

Therapeutic Classes:
- Central Nervous System (CNS) Stimulants (armodafinil, modafinil)
- Histamine-3 (H_3) Receptor Antagonist/Inverse Agonist (pitolisant)
- CNS Depressants (sodium oxybate/oxybate salts)
- Dopamine and Norepinephrine Reuptake Inhibitor (DNRI) (solriamfetol)

Purpose of Review: To evaluate the safety and efficacy of agents used for narcolepsy, including the new formulation, Xywav (oxybate salts), for formulary consideration.

* Brand names are indicated by bolded text; generic-only products are indicated by non-bolded text

Note: Information on indications, pharmacology, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

SUMMARY

Background

- Narcolepsy is a chronic neurological disorder of hypersomnia and its associated symptoms are potentially debilitating. Narcolepsy is typically classified as type 1 (narcolepsy with cataplexy) or type 2 (narcolepsy without cataplexy) (*Bhattarai & Sumerall 2017, Szabo et al 2019*). Narcolepsy type 1 is estimated to have a prevalence of 25 to 50 per 100,000 people. Narcolepsy typically begins in the teens and early twenties, but occasionally occurs as early as age 5 or after age 40. The prevalence of narcolepsy type 2 is uncertain, as it is less well studied and more difficult to diagnose; however, it has been estimated as 20 to 34 per 100,000 people (*Scammel 2020a*). Excessive daytime sleepiness (EDS) is present in all patients with narcolepsy. Other symptoms include cataplexy, hypnagogic hallucinations, and sleep paralysis; however, only about one-third of patients have all 4 symptoms (*Scammell 2020a*). Patients may also experience fragmented nighttime sleep. Patients with narcolepsy have been shown to be at increased risk for cardiovascular (CV), metabolic, and psychiatric comorbidities compared with individuals without narcolepsy (*Xywav dossier 2020*). Pharmacological interventions are the most common approach for treating narcolepsy. Current medications have been developed to target symptoms; however, most patients do not experience complete resolution despite receiving optimal standard treatment (*Bhattarai & Sumerall 2017, Scammell 2020b).*
- Obstructive sleep apnea (OSA) is a disorder that is characterized by obstructive apneas and hypopneas caused by repetitive collapse of the upper airway during sleep. The diagnosis should be considered whenever a patient presents with symptoms such as EDS, snoring, and choking or gasping during sleep, particularly in the presence of risk factors such as obesity, male gender, and advanced age (*Kline 2019*). Besides EDS, untreated OSA has many potential adverse clinical consequences including impaired daytime function, metabolic dysfunction, and an increased risk of CV disease and mortality. All patients diagnosed with OSA should be offered positive airway pressure (PAP) as initial therapy. Continuous positive airway pressure (CPAP) involves maintenance of a positive pharyngeal transmural pressure so that the intraluminal pressure exceeds the surrounding pressure. CPAP also stabilizes the upper airway through increased end expiratory lung volume. As a result, respiratory events due to upper airway collapse (eg, apneas, hypopneas) are prevented. Other options to PAP include oral appliances or upper airway surgery in severe cases with a surgically correctable upper airway obstruction. Wakefulness-promoting pharmacological agents (eg,

modafinil, armodafinil) may be beneficial as adjunctive therapy for EDS that persists despite adequate and successful conventional OSA therapy (*Kryger 2020*).

- Shift work disorder (SWD) is a circadian rhythm sleep disorder that occurs in individuals who work night shifts. These individuals commonly experience difficulties with both sleep and alertness at desired times, and shift work is increasingly recognized as a risk factor for a variety of adverse health outcomes, including diabetes, cancer, and CV disease. While some shift workers show circadian adjustment to their work schedule, most do not. Up to one-third of shift workers report regular, persistent complaints of insomnia and/or excessive sleepiness that meet formal criteria for SWD (ie, development of sleep disturbances and impairment of waking alertness and performance) (*Cheng & Drake 2019, Morgenthaler et al 2007b*). Minimum measures to improve sleep after a night shift include a regular sleep schedule (ie, "anchor sleep"), light-blocking shades, and ambient noise control. Treatment with modafinil or armodafinil is an option in patients with persistent sleepiness in conjunction with nonpharmacologic measures to improve sleep and alertness. The magnitude of benefit may vary among individuals. The observed benefits in randomized controlled trials (RCTs) have been modest, however, and adverse effects (AEs) may outweigh benefits in some patients (*Cheng & Drake 2019*).

Indications

- Provigil/Nuvigil
  - Provigil (modafinil) received Food and Drug Administration (FDA) approval to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy in December 1998; approval was granted for OSA and SWD in January 2004 (*FDA Web site*).
  - Nuvigil (armodafinil), the R-enantiomer of modafinil, was approved as a new formulation in June 2007 to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or SWD (*FDA Web site*).
  - Modafinil and armodafinil are both Schedule IV controlled substances.
- Sunosi (solriamfetol), received FDA approval in March 2019 to improve wakefulness in adult patients with EDS associated with narcolepsy or OSA (*FDA Web site*). Solriamfetol has orphan drug designation in the U.S. for narcolepsy (*Sunosi press release 2019*). Solriamfetol is a Schedule IV controlled substance.
- Wakix (pitolisant), received FDA approval on August 15, 2019 for the treatment of EDS in adults with narcolepsy with orphan and priority review designations. In October 2020, pitolisant gained approval for the additional indication of cataplexy in adults. Pitolisant has shown no abuse potential and is the only unscheduled agent indicated for the treatment of narcolepsy and narcolepsy-cataplexy (*FDA web site*).
- Xyrem/Xywav
  - Xyrem (sodium oxybate) was approved in July 2002 with orphan drug status under priority review for the treatment of cataplexy associated with narcolepsy. Use of Xyrem was expanded to the pediatric population in October 2018 (*FDA Web site*). Xyrem is indicated for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy. A new formulation of oxybate salts, Xywav, received FDA approval in July 2020 for the same indication as Xyrem (*FDA Web site, Xywav dossier 2020*). Xywav contains the same active moiety as Xyrem but is made up of a unique composition of cations (calcium, magnesium, potassium, and sodium oxybates) that contains 92% less sodium than Xyrem at all nightly doses. Xyrem and Xywav are Schedule III controlled substances (*Xywav dossier 2020*).
    - The recommended daily adult dose of Xyrem (6 to 9 g/night) adds 1100 to 1640 mg of sodium to total daily intake, which accounts for 73 to 109% of the total daily sodium intake (no more than 2300 mg and ideally < 1500 mg for most adults) recommended by the American Heart Association (AHA) (*AHA 2017*). The Xyrem product labeling includes a warning regarding the high sodium content and advises monitoring of symptoms and daily sodium intake in patients sensitive to salt intake (eg, those with heart failure [HF], hypertension [HTN], or renal impairment) (*Xyrem prescribing information 2020*).

Pharmacology

- The mechanism(s) through which modafinil/armodafinil promotes wakefulness is unknown, but may involve increased dopaminergic signaling through blocking of dopamine reuptake in a manner distinct from amphetamines (*Scammell 2020a*).
  - PK studies have shown that R-modafinil has a longer half-life than S-modafinil (10 to 14 vs 3 to 4 hours). Additionally, it has been reported that the elimination of S-modafinil is 3 times faster than that of R-modafinil. Because R-modafinil has a longer half-life than modafinil, its administration results in higher plasma concentrations later in the waking day compared with modafinil on a ''mg-to-mg'' basis (*Harsh et al 2006*).
- The mechanism of action of pitolisant in EDS in adult patients with narcolepsy is unclear. However, its efficacy could be mediated through its activity as an antagonist/inverse agonist at histamine-3 (H_3) receptors.
- Sodium oxybate is a central nervous system (CNS) depressant. Its mechanism of action in the treatment of narcolepsy is unknown. Xyrem (sodium oxybate) is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous compound

and metabolite of the neurotransmitter gamma-aminobutyric acid (GABA). Oxybate salts is a mixture of calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate. It is hypothesized that the therapeutic effects of sodium oxybate and oxybate salts on cataplexy and EDS are mediated through GABA actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons (*Xywav prescribing information 2020*).

- Solriamfetol is a selective dopamine and norepinephrine reuptake inhibitor (DNRI) with wake-promoting effects (*Scammell 2020a*).

Clinical Efficacy

- Efficacy measures
  - Objective measures of EDS as assessed by sleep latency (ie, the time interval between attempting to fall asleep and the onset of sleep) measured using polysomnography (PSG):
    - Maintenance of Wakefulness Test (MWT) (*Freedman 2019*)
      - The MWT measures an individual's ability to remain awake during the daytime in a darkened, quiet environment. Patients are instructed to remain awake for as long as possible during serial 40-minute test sessions, and sleep latency is determined as the mean number of minutes patients could remain awake in the first 4 test sessions. Among healthy individuals, the mean sleep latency is approximately 30 minutes, with > 97% of individuals having a mean sleep latency ≥ 8 minutes; thus, a mean sleep latency < 8 minutes is generally considered abnormal. Staying awake for at least 40 minutes during all 4 sessions is strong objective evidence that an individual can stay awake. A mean sleep latency between 8 and 40 minutes has uncertain significance.
    - Multiple Sleep Latency Test (MSLT) (*American Sleep Association Web site, Thorpy 1992*)
      - The MSLT also measures an individual's ability to remain awake during the daytime in ideal quiet conditions. The MSLT consists of 5 nap opportunities to determine both severity of sleepiness and presence of 2 or more sleep onset rapid eye movement (REM) periods. The absence of sleep on any nap opportunity is recorded as a sleep latency of 20 minutes. A mean sleep latency of 0 to 5 minutes indicates severe sleepiness, while 5 to 10 minutes is rated as moderate sleepiness.
  - Subjective measures of EDS:
    - Epworth Sleepiness Scale (ESS) (*Johns 1991*)
      - The ESS is an 8-item questionnaire by which patients rate their perceived likelihood of falling asleep during usual daily life activities.
      - The score ranges from 1 to 24 points; 9 to 24 points indicates abnormal (possibly pathologic) sleepiness.
    - Clinical Global Impression of Change (CGI-C)
      - The CGI-C is a 7-point physician-rated scale that assesses symptom severity and treatment response (range: 1 [very much improved] to 7 [very much worse]).
    - Patient Global Impression of Change (PGI-C)
      - The PGI-C is a 7-point patient-rated scale that assesses their symptom change from baseline (range: 1 [very much improved] to 7 [very much worse]).
  - Sustained Attention to Response Task (SART) (*Fronczek et al 2006*)
    - The SART is an objective laboratory measure of sustained vigilance and attention. Patients are presented with a series of numbers (ranging from 1 to 9) 225 times. Patients must press a button except when the number presented is 3. The SART comprises 3 error scores: the number of times a button was pressed inappropriately ("NO GO"), the number of times key pressing was missed ("GO"), and the sum of these 2 scores.
- Modafinil/armodafinil:
  - A systematic review and meta-analysis (9 RCTs, N = 1054) was conducted to evaluate the efficacy and safety of modafinil (any dose or regimen) vs no active treatment or other drugs in the treatment of narcolepsy (*Golicki et al 2010*). The primary endpoints were elimination of EDS assessed by objective laboratory tests (MSLT, MWT) or validated subjective outcome measures (ESS) and number and duration of severe somnolence, sleep attacks and naps, as reported by patients.
    - Compared with placebo, modafinil significantly increased mean sleep latency assessed by the MSLT (3 studies): weighted mean difference (WMD) 1.11 minutes (95% confidence interval [CI], 0.55 to 1.66); I^2 = 0%; test for overall effect: Z = 3.90 (p < 0.0001). As assessed by the MWT (6 studies), there was a greater increase in mean sleep latency with modafinil vs placebo: WMD 2.82 minutes (95% CI, 2.40 to 3.24); I^2 = 0%; test for overall effect: Z = 13.14 (p < 0.00001). Compared with placebo, modafinil significantly reduced the ESS score (6 studies): WMD -2.73 points (95% CI, -3.39 to -2.08); I^2 = 0%; test for overall effect: Z = 8.17 (p < 0.00001). Modafinil also improved the number (p = 0.006) and duration (p = 0.03) of severe somnolence episodes, sleep attacks, and naps per day as compared with placebo, but did not reduce the number of cataplexy attacks per day (4 studies): WMD 0.02 (95% CI, -0.27 to 0.31); I^2 = 71%; test for overall effect: Z = 0.13 (p = 0.90). Quality of life (QoL) as measured by the Short Form (SF)-36 and validated narcolepsy-specific questionnaire (2 studies) indicated

significant improvement with modafinil vs placebo in 5 out of 7 narcolepsy-specific domains, SF-36 mental health summary scale and 4 (modafinil 200 mg/day) or 5 (modafinil 400 mg/day) SF-36 domains.

- A 12-week, Phase 3, double-blind (DB), placebo-controlled (PC), multicenter (MC) RCT (N = 196) assessed the efficacy and safety of armodafinil for the treatment of EDS in patients with narcolepsy (*Harsh et al 2006*). Patients were randomized to either armodafinil 150 or 250 mg once daily. The co-primary endpoints were change from baseline in mean sleep latency on the MWT 9:00 AM to 3:00 PM and the proportion of patients with at least minimal improvement on the physician-rated CGI-C.
  - At the final visit, mean MWT 9:00 AM to 3:00 PM sleep latency increased 1.3, 2.6, and 1.9 minutes from baseline in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.9 minutes from baseline in the placebo group. Treatment differences from placebo were 3.2, 4.5, and 3.8 minutes in the 150 mg, 250 mg, and armodafinil combined groups, respectively (all $p < 0.01$). The proportion of patients with at least minimal improvement in the CGI-C was significantly higher for the armodafinil 150 mg, 250 mg, and combined groups compared with placebo at all time points during the study ($p < 0.0001$ for both individual doses and the combined group vs placebo at final visit). The proportion of patients rated as minimally, much, and very much improved on the CGI-C from baseline to final visit was 21%, 33% and 16%, respectively, for armodafinil 150 mg; 20%, 35%, and 18%, respectively, for armodafinil 250 mg; 20%, 34%, and 17%, respectively, for the armodafinil combined group; and 17%, 12%, and 3%, respectively, for placebo. Armodafinil 150 and 250 mg/day reduced the mean daily number of unintended sleep episodes by 33% and 44%, respectively, compared with a 10% reduction in the placebo group ($p < 0.0001$ for overall treatment comparison). The mean number of daily naps was reduced by 41%, 44%, and 22%, respectively, for the armodafinil 150 mg, armodafinil 250 mg, and placebo groups ($p = 0.0039$ for overall treatment comparison). The mean number of mistakes/near misses/accidents was reduced by 43% and 30% in the armodafinil 150 mg and 250 mg groups, respectively, compared with a 10% reduction in the placebo group; however, these differences were not statistically significant ($p = 0.1792$ for overall treatment comparison).
- A systematic review and meta-analysis (11 modafinil RCTs [N = 723] and 5 armodafinil RCTs [N = 1009]) evaluated the efficacy of modafinil and armodafinil in treating EDS in patients with OSA (*Kuan et al 2016*). Most trials investigated whether modafinil or armodafinil with concurrent CPAP use improved sleepiness, neurocognitive performance, and functional outcome in patients with sleep apnea. The primary endpoints were sleep latency assessed by the MSLT or MWT, ESS, Karolinska Sleepiness Scale (KSS), and Stanford Sleepiness Scale (SSS).
  - ESS scores in patients receiving CPAP were significantly reduced with modafinil (5 RCTs, WMD, -2.95 [95% CI, -3.73 to -2.17]) and armodafinil (4 RCTs, WMD, -2.78 [95% CI, -3.51 to -2.05]) compared with placebo ($I^2 = 0\%$). Sleep latency assessed by the MWT was significantly increased in the modafinil group (WMD, 2.51 [95% CI, 1.5 to 3.52]) and in the armodafinil group (WMD, 2.71 [95% CI, 0.02 to 5.37]) vs placebo. However, a meta-analysis of data from 3 RCTs that compared the effects of modafinil and placebo on sleep latency, as assessed by the MSLT found no significant differences. Four studies evaluated the effects of modafinil on subjective sleepiness during acute CPAP withdrawal or in CPAP-naïve patients with OSA. There was a significant reduction in daytime sleepiness duration ($p < 0.05$), significant improvements on the ESS ($p = 0.003$), KSS ($p = 0.04$ and $p = 0.01$), SSS ($p = 0.03$), and daytime sleepiness visual analog scale ($p = 0.01$). A non-significant trend of improved self-reported sleepiness on the ESS after armodafinil use among patients with OSA before CPAP treatment was observed in 1 study ($p = 0.066$). The proportion of patients with improvement on the CGI-C was evaluated in 3 RCTs of modafinil and 4 RCTs of armodafinil. There was significant improvement in both the modafinil and armodafinil groups vs the placebo group, with pooled risk ratios (RR) of 1.94 (95% CI, 1.53 to 2.44) and 1.48 (95 % CI, 1.17 to 1.87), respectively. The results on neurocognitive performance were inconsistent.
- A 3-month, Phase 3, DB, PC, MC RCT (N = 209) investigated the efficacy and safety of modafinil for the treatment of sleepiness in patients with SWD (*Czeisler et al 2005*). Patients received modafinil 200 mg 30 to 60 minutes before each night shift. The primary endpoints were the CGI-C rating for sleepiness during the night shift, including the commute to and from work, at the final visit and change between baseline and the final visit in overall mean sleep latency based on nighttime MSLT.
  - Seventy-four percent of patients in the modafinil group were rated as at least minimally improved on the CGI-C at the final visit, as compared with 36% in the placebo group ($p < 0.001$). Overall mean sleep latency, as measured by the MSLT, increased from 2.1 minutes at baseline to 3.8 minutes at the final visit with modafinil (change, 1.7 minutes; $p < 0.001$) but not with placebo (2.04 at baseline vs 2.37 at the final visit; change, 0.3; $p = 0.24$). Sleep latency was significantly greater in the modafinil group than in the placebo group ($p = 0.002$). This improvement in sleep latency with modafinil vs placebo was found at 2:00 AM ($p = 0.02$) and 4:00 AM ($p < 0.001$), but not at 6:00 AM ($p = 0.45$) or 8:00 AM ($p = 0.17$). Patients who were receiving modafinil also had a reduction in the frequency and duration of lapses of attention during nighttime testing of their performance on the Psychomotor Vigilance Test (change from baseline, a reduction in lapse frequency of 2.6 vs an increase of 3.8, respectively; $p < 0.001$), and fewer proportions of patients reported having had accidents or near accidents while commuting home (29%

vs 54%, respectively; < 0.001). Despite these benefits, patients treated with modafinil continued to have excessive sleepiness and impaired performance at night.

- A 12-week, DB, PC, MC RCT (N = 254) assessed the effect of armodafinil on the physiologic propensity for sleep and cognitive performance during usual night shift hours in patients with excessive sleepiness associated with chronic moderate to severe SWD (*Czeisler et al 2009*). The primary endpoints were change from baseline to final visit in overall mean sleep latency as assessed by the MSLT and the proportion of patients with at least minimal improvement in the CGI-C during the night shift and commute to and from work at the final visit.
  - Armodafinil significantly improved mean sleep latency from 2.3 minutes at baseline to 5.3 minutes at final visit, compared with a change from 2.4 minutes to 2.8 minutes in the placebo group (p < 0.001). A total of 89 (79%) armodafinil patients were rated as improved on the CGI-C at the final visit compared with 61 (59%) of the placebo patients (p = 0.001). At the final visit, armodafinil was associated with significant improvement as reported in patient diaries, including maximum level of sleepiness during the night shift (p < 0.001) and commute home (p = 0.003) and the mean number of mistakes, accidents, or near misses during the night shift (p = 0.004), but not during the commute home (p = 0.12) compared with placebo.
- A 40-week, open-label (OL) extension study assessed the long-term efficacy and safety of modafinil in 478 patients with EDS associated with narcolepsy who completed 1 of the 2 pivotal 9-week RCTs of modafinil (*Mitler et al 2000*). A flexible-dose regimen (ie, 200, 300, or 400 mg daily) was followed in 1 study. In the second study, patients received 200 mg/day for 1 week, followed by 400 mg/day for 1 week, then either 200 or 400 mg doses for the duration of the study; the majority (~75%) received 400 mg/day.
  - Disease severity improved in > 80% of patients throughout the 40-week study. At weeks 2, 8, 24, and 40, disease severity was “much improved” or “very much improved” in 49, 58, 59, and 58% of patients, respectively. The mean ESS score improved significantly from 16.5 at OL baseline to 12.4 at week 2 and remained at that level through week 40 (p < 0.001). QoL scores at weeks 4, 8, 24, and 40 were significantly improved vs OL baseline scores for 6 of the 8 SF-36 domains (p < 0.001). The most common treatment-related AEs were headache (13%), nervousness (8%), and nausea (5%). Most AEs were mild to moderate. Forty-three patients (9.0%) discontinued treatment because of AEs.
- The long-term efficacy and safety of armodafinil in patients with EDS associated with treated OSA, SWD, or narcolepsy who completed one of four 12-week pivotal RCTs were assessed in a 12-month, flexible-dose (50 to 250 mg/day), OL extension study. Of 743 enrolled patients (474 with treated OSA, 113 with SWD, and 156 with narcolepsy), 57% of patients completed 12 months or more of treatment (*Black et al 2010*).
  - Compared with baseline, minimal or greater improvement on the CGI-C was reported by most patients in the 3 diagnostic groups (75% to 92%) at final visit; patients in the SWD group reported the greatest improvement. A rating of much or very much improved was reported at the final visit by 65% (295/457) of patients with treated OSA (95% CI, 60.2 to 68.9), 88% (92/105) with SWD (95% CI, 81.3 to 93.9), and 62% (93/150) with narcolepsy (95% CI, 54.2 to 69.8). At baseline, the proportion of patients with a normal ESS score (ie, < 10) was 0.4% (2/454) in the treated OSA group and 3.4% (5/147) in the narcolepsy group. At the final visit, the mean ESS score was reduced by 6.4 (95% CI, -6.90 to -5.94) in the treated OSA group and by 4.3 (95% CI, -5.20 to -3.49) in the narcolepsy group. The proportion of patients with an ESS score < 10 at final visit was 54.8% (249/454) for treated OSA and 31.3% (46/147) for narcolepsy. At final visit, mean global Brief Fatigue Inventory (BFI) scores were reduced by 1.7 (95% CI, -1.88 to -1.43) in the treated OSA group, 2.3 (95% CI, -2.75 to -1.87) in the SWD group, and 1.7 (95% CI, -2.13 to -1.35) in the narcolepsy group; mean worst fatigue scores were reduced by 1.8 (95% CI, -2.13 to -1.57) in the treated OSA group, 2.4 (95% CI, -3.06 to -1.83) in the SWD group, and 1.5 (95% CI, -2.00 to -1.07) in the narcolepsy group. The most commonly reported AEs were headache (25%), nasopharyngitis (17%), insomnia (14%), and upper respiratory tract infection (10%). Most AEs were mild or moderate.

- Pitolisant:
  - The efficacy and safety of pitolisant were evaluated in two Phase 3, active-controlled, DB, PC, MC pivotal RCTs conducted in Europe/South America evaluating the treatment of EDS in adults with narcolepsy with or without cataplexy (HARMONY 1 and HARMONY 1bis) (*Dauvilliers et al 2013*, *Wakix dossier 2019, Wakix FDA clinical review 2019*). Both studies included an 8-week treatment period which consisted of a 3-week dose titration phase followed by a 5-week stable dose phase. During the 3-week flexible dosing period, the dose was determined according to the investigator’s judgement based on individual clinical efficacy and safety. The primary endpoint was the difference in change in ESS scores between the pitolisant and placebo groups at 8 weeks. In both trials, superiority of pitolisant over placebo was tested first, then, if shown to be superior, the non-inferiority of pitolisant vs modafinil was tested based on a non-inferiority margin of 2 ESS points.
    - In HARMONY 1 (*Dauvilliers et al 2013*), 95 patients were randomized to receive pitolisant 10, 20, or 40 mg (expressed as salt form; equivalent to 8.9, 17.8, and 35.6 mg) per day; modafinil 100, 200, or 400 mg per day; or placebo. Of the 94 patients in the intent-to-treat (ITT) analysis, 81% had cataplexy, 45% had received psychostimulants (mostly modafinil or methylphenidate) and 35% were receiving anticataplectic drugs and continued them at stable doses during the trial (sodium oxybate, n = 8; antidepressants, n = 25).

- The primary analysis of between-group differences in mean ESS score at endpoint (adjusted for baseline) showed pitolisant to be superior to placebo (mean difference [MD] -3.0; 95% CI, -5.6 to -0.4; p = 0.024), but not non-inferior to modafinil (MD 0.12; 95% CI, -2.5 to 2.7; p = 0.250).
- A post-hoc analysis of ESS responder rate (final ESS score ≤ 10) showed a significantly greater response with pitolisant vs placebo (13 vs 45%; MD 4.4 [95% CI, 2.1 to 9.2]; p < 0.0006) and a similar response between pitolisant and modafinil (45 vs 46%; MD 1.0 [95% CI, 0.68 to 1.6]; p = 0.908).
- MWT values decreased from baseline in the placebo group but improved in the pitolisant group demonstrating superiority of pitolisant (MD 1.47; 95% CI, 1.01 to 2.14; p = 0.044). MWT also improved from baseline in the modafinil group. There was no statistically significant difference between pitolisant and modafinil (MD 0.77; 95% CI, 0.52 to 1.13; p = 0.173).
- NO GO error scores in the SART were similar between baseline and end of treatment in the placebo group, whereas they decreased in the pitolisant group, with a statistically significant difference between groups (p = 0.038). Changes in the modafinil and pitolisant groups were not statistically different (p = 0.765). There were no differences in changes from baseline between either pitolisant and placebo or pitolisant and modafinil in either the SART GO scores (p = 0.176, p = 0.141) or total SART scores (p = 0.053; p = 0.370).
- The European Quality-of-Life Questionnaire (EQ-5D) values were similar in all 3 groups, whereas patient global impression on treatment (PGO) improved only slightly more for pitolisant or modafinil than for placebo.
- In post-hoc analyses, pitolisant was superior to placebo (MD 0.38; 95% CI, 0.16 to 0.93; p = 0.034) but not non-inferior to modafinil (MD 0.54; 95% CI, 0.24 to 1.23; p = 0.138) for improvement in daily cataplexy rate from baseline.
- AEs occurred in 22 patients receiving pitolisant, 26 receiving modafinil, and 10 receiving placebo. The most frequent AEs were headache for the 3 groups; insomnia, abdominal discomfort, and nausea for pitolisant; and abdominal discomfort, nausea, diarrhea, dizziness, anxiety, and irritability for modafinil.

▪ HARMONY 1bis (unpublished) (*Wakix dossier 2019, Wakix FDA clinical review 2019*) compared pitolisant titrated to a maximum dose of 20 mg per day, modafinil 200 to 400 mg per day, and placebo in 166 patients. Of the 164 patients included in the extended ITT population, a history of cataplexy was present in 50 (75%) patients in the pitolisant group, 50 (77%) in the modafinil group, and 26 (81%) in the placebo group. Patients with severe cataplexy were allowed to remain on their anticataplectic medication at a stable dose except tricyclic antidepressants (TCAs).

- The pitolisant group had a significantly greater ESS score improvement from baseline compared with placebo, demonstrating superiority. The mean change from baseline in ESS score (± standard deviation [SD]) was -4.5 (4.6) for pitolisant and -3.7 (5.6) for placebo (treatment effect: -2.12; 95% CI, -4.10 to -0.14; p = 0.036). The mean change from baseline in ESS score (±SD) was -7.8 (5.8) for modafinil; the non-inferiority of pitolisant compared to modafinil could not be concluded (treatment effect: 2.83; 95% CI, 1.10 to 4.55; p = 0.002), most likely due to an imbalance between dosages of both drugs and the short treatment period.
  - The upper dose of pitolisant was limited to 20 mg daily (one-half the maximum dose allowed in other trials), while modafinil was titrated up to the recommended dosing of 200 mg or 400 mg daily.
- The ESS responder rate (final ESS score ≤ 10 or ESS score reduction ≥ 3) was significantly greater in the pitolisant group (64.2%) compared to the placebo group (34.4%) (RR 2.10; p = 0.002). There was no significant difference between pitolisant and modafinil (64.2% vs 76.9%; RR 0.86; p = 0.052).
- MWT values decreased from baseline in the placebo group but improved in the pitolisant group (p = 0.022). MWT also improved from baseline in the modafinil group; however, no statistically significant difference between pitolisant and modafinil was seen (p = 0.198).
- The NO GO error scores in the SART decreased in the pitolisant group, with a statistically significant treatment difference compared with placebo (p = 0.002); changes in the modafinil and pitolisant groups were not statistically different.
- Differences in weekly cataplexy rate (WCR) between pitolisant and placebo were not significant (MD -1.00; 95% CI, -2.12 to 0.13; p = 0.077), nor were the differences between pitolisant and modafinil (MD 0.05; 95% CI, -0.55 to 0.65; p = 0.865).
- The most frequent AEs were headache in all 3 groups; nausea, nasopharyngitis, and dizziness in the pitolisant group; nasopharyngitis in the modafinil group; and dizziness, diarrhea, insomnia, and fatigue in the placebo group.

○ The efficacy and safety of pitolisant on cataplexy in 106 patients with narcolepsy were evaluated in a DB, PC, MC RCT (HARMONY CTP; *Szakacs et al 2017*). Patients received 3 weeks of flexible dosing (5, 10, or 20 mg as determined by the investigator based on efficacy and tolerance) followed by 4 weeks of stable dosing (5, 10, 20, or 40 mg). The primary endpoint was the change in the average number of cataplexy attacks per week as recorded in patient diaries (ie, the WCR between the 2-week baseline period and the 4-week stable dosing period). The cataplexy reduction was measured by the ratio $WCR_{f/b} = WCR_f/WCR_b$.

- In the stable dosing phase, 64.8% of patients (35/54) in the pitolisant group received the maximum dose of 40 (35.6) mg.
- From a baseline WCR of 9.15 in the pitolisant group and 7.31 in the placebo group, the WCR was significantly reduced by a relative 75% in the pitolisant group (final WCR = 2.27; $WCR_{f/b}$ = 0.25) compared with 38% in the placebo group (final WCR = 4.52; $WCR_{f/b}$ = 0.62; rate ratio [rR] = 0.51; 95% CI, 0.44 to 0.60; p < 0.0001).
  - In post-hoc analyses, this effect remained significant (all p < 0.0001) for each subgroup of patients receiving 10 mg (n = 7), 20 mg (n = 9), or 40 mg (n = 35) as their stable dose.
  - In a pre-specified analysis, the effect of pitolisant was unchanged, irrespective of whether patients used concomitant anticataplectic treatment pre-inclusion. The geometric mean of the ratio $WCR_{f/b}$ for patients who were receiving concomitant anticataplectic treatment (rR 0.49; 95% CI, 0.31 to 0.82; n = 12) or did not receive this medication (rR 0.51; 0.11 to 2.28; n = 93) were not significantly different ($p_{interaction}$ = 0.455).
- For almost all secondary endpoints, a significant superiority of pitolisant was shown (ie, proportion of patients with WCR > 15 at the end of treatment, mean ESS decrease, patient proportion with final ESS ≤ 10, MWT mean change, CGI-C, PGO, and frequency of hallucinations).
- The proportion of patients reporting AEs did not differ significantly between those receiving pitolisant and those receiving placebo (31% for pitolisant vs 35% for placebo); however, double the number of AEs were considered treatment-related with pitolisant compared with placebo (28% for pitolisant vs 12% for placebo; p = 0.048). The most frequent AEs were headache for both treatment groups; irritability, anxiety, and nausea for the pitolisant group; and somnolence for the placebo group.

○ A 12-month, OL, MC, uncontrolled longitudinal study (HARMONY 3) was conducted to evaluate the long-term safety of pitolisant (*Dauvilliers et al 2019*). In addition, a 5-year extension of HARMONY 3 was conducted in the French cohort of patients. A total of 102 patients were treated. Sixteen patients were already treated through the authorization for temporary use (ATU) and 86 patients were naïve to pitolisant.

- In the 12-month analysis (N = 68; 34 prematurely withdrew), the mean change from baseline in ESS score (±SD) was -4.63 (4.91) and about two-thirds (44/68) of patients who completed the study were ESS responders (final ESS score ≤ 10 or ESS score reduction ≥ 3). On the CGI-C scale, investigators rated 94.1% of patients who completed 12 months of treatment as improved. The number of complete (generalized) cataplexy attacks per day decreased by 76% between baseline (0.33) and 12 months (0.08) in the subgroup of 44 patients with completed sleep diaries through the 12-month visit; the number of partial cataplexy attacks per day decreased by 65% between baseline (0.77) and 12 months (0.27). The most frequently reported treatment-emergent AEs (TEAEs) were headache (11.8%), insomnia (8.8%), weight gain (7.8%), anxiety (6.9%), depression (4.9%) and nausea (4.9%).
- In the 5-year extension, the decrease in ESS score (±SD) achieved by the study population at the end of the first 12-month period was maintained and continued during the extended follow-up period, with -4.41 (5.38) after 2 years of treatment (n = 45), -4.45 (6.16) after 3 years of treatment (n = 38), -4.76 (5.73) after 4 years of treatment (n = 34), and -6.07 (7.19) after 5 years of treatment (n = 14). The most commonly reported TEAEs were headache (19.5%), weight gain (18.2%), insomnia (11.7%), anxiety (11.7%), depression (11.7%), and nausea (11.7%) (*Wakix dossier 2019*).
- No new safety signals were identified during long-term exposure to pitolisant for up to 5 years compared with the safety profile identified in previous RCTs.

○ A postmarketing observation study in Europe is ongoing and will follow patients for up to 5 years. The AE profiles in these long-term studies, and in the European postmarketing databases, are similar to the AE profile observed during the short-term clinical trials. Of note, fewer than 100 patients with narcolepsy have received the proposed highest recommended dose of pitolisant (35.6 mg). However, narcolepsy is an orphan indication and no clear association between dose and AEs was evident from the narcolepsy clinical trials (*Wakix FDA summary review 2019*).

- Sodium oxybate/oxybate salts:

○ A systematic review and meta-analysis (N = 6 RCTs and 5 companion reports, N = 741) evaluated the efficacy and safety of sodium oxybate in narcolepsy-cataplexy patients (*Alshaikh et al 2012*). Included trials ranged from 4 to 12 weeks in duration. The dose of sodium oxybate was between 4.5 to 9 g per night in most of the studies. The primary endpoint was elimination of EDS according to subjective or objective indicators.

- Sodium oxybate (usually 9 g/night) was superior to placebo for reducing mean weekly cataplexy attacks (n = 2 RCTs, MD: -8.46, 95% CI, -15.27 to -1.64), heterogeneity: I^2 = 0%, test for overall effect: Z = 2.43 [p = 0.01]); increasing the MWT (n = 2 RCTs, MD: 5.18, 95% CI, 2.59 to 7.78, I^2 = 0%, Z = 3.93 [p < 0.0001]); and reducing sleep attacks (n = 2 RCTs, MD: -9.65, 95% CI, -17.72 to -1.59), I^2 = 13%, Z = 2.35 [p = 0.02]). Data from 3 RCTs indicated an increase in CGI-C scores (RR: 2.42, 95% CI, 1.77 to 3.32, I^2 = 0%, Z = 5.53 [p < 0.00001]). Sodium oxybate did not significantly increase REM sleep vs placebo (n = 2 RCTs, MD: -0.49, 95% CI, -3.90 to 2.92, I^2 = 0%, Z = 0.28 [p = 0.78]). Patients receiving sodium oxybate (9 g per night) experienced more AEs vs placebo,

including nausea (p < 0.00001), vomiting (p = 0.09), dizziness (p = 0.02) and enuresis (p = 0.03); most AEs were mild or moderate.

- A DB, PC, PG, MC RCT (N = 222) assessed the efficacy of sodium oxybate, modafinil, and the combination of the two for EDS in narcolepsy patients previously taking modafinil (*Black & Houghton 2006*). Patients received unchanged doses of modafinil (with sodium oxybate placebo) during a 2-week baseline phase. Following a baseline PSG and MWT, they were randomly assigned to 1 of 4 treatment groups: sodium oxybate placebo plus modafinil placebo, sodium oxybate plus modafinil placebo, modafinil plus sodium oxybate placebo, or sodium oxybate plus modafinil. Sodium oxybate was administered as 6 g nightly for 4 weeks and was then increased to 9 g nightly for 4 additional weeks. The primary endpoint was the MWT; secondary endpoints included ESS score and the CGI-C.
  - Following the switch from modafinil to placebo, the mean average daytime sleep latency on the MWT decreased from 9.74 minutes at baseline to 6.87 minutes after 8 weeks (p < 0.001). In the sodium oxybate group, there was no difference (from 11.29 to 11.97 minutes) suggesting that sodium oxybate was as effective as the previously administered modafinil. In contrast, the sodium oxybate-modafinil group demonstrated an increase in daytime sleep latency from 10.43 minutes to 13.15 minutes (p < 0.001), suggesting an additive effect. The sodium oxybate group also demonstrated a decrease in median average ESS scores, from 15 to 12.0, whereas the sodium oxybate-modafinil group decreased from 15.0 to 11.0 (p < 0.001 for each from baseline). In the sodium oxybate group, sleep attacks decreased from a mean of 10.05 at baseline to 7.10 after 8 weeks (p < 0.001) and the sodium oxybate-modafinil group demonstrated a decrease from 11.82 to 5.55 (p < 0.001). There was no significant difference between the modafinil- and placebo-treated groups. Compared with the placebo group, 48.0% (p = 0.002) of the sodium oxybate group and 46.3% (p = 0.023) of the sodium oxybate-modafinil group were judged to be much improved or very much improved on the GCI-C, compared with 21.8% in the placebo group and 19% in the modafinil group.
- Patients with narcolepsy-cataplexy (N = 55) who had received sodium oxybate for ≥ 6 months (range, 7 to 44 months, mean 21 months) in a long-term, OL sodium oxybate safety trial were enrolled in a DB treatment withdrawal study (*U.S. Xyrem Multicenter Study Group 2004*). Patients were previously stabilized on sodium oxybate using individualized doses providing optimum clinical effect, ranging from 3 to 9 g nightly. A 2-week single-blind (SB) sodium oxybate treatment phase established a baseline for the weekly occurrence of cataplexy. This was followed by a 2-week DB phase in which patients were randomized to receive unchanged drug therapy (n = 26) or placebo (n = 29). The primary endpoint was the change in the number of weekly cataplexy attacks from the baseline to the DB treatment phase.
  - In the sodium oxybate group, there was no median change in the number of cataplexy attacks between the 2-week SB baseline phase and the 2-week DB phase. In contrast, cataplexy attacks increased by a median of 21.0 in the placebo patients during the same 2-week period (p < 0.001); median change from baseline was 39.0 for the placebo group and 16.5 for the sodium oxybate group. The mean frequency of weekly cataplexy attacks over the 2-week baseline period increased from 15.8 to 46.4 at the end of the 2-week DB phase for patients receiving placebo; in patients receiving sodium oxybate, the number of cataplexy episodes was 9.9 and 12.8 at the same time points. There was no evidence of rebound cataplexy in patients who were randomized to placebo following long-term use of sodium oxybate. During the SB phase of the study, AEs were reported in 17 (31%) patients. During the DB phase, AEs were reported by 12 (22%) patients, including 3 patients in the sodium oxybate group, and 9 in the placebo group. No AE led to discontinuation and none were serious.
- The efficacy of sodium oxybate in the treatment of cataplexy and EDS in pediatric patients with narcolepsy was established in a DB, PC, randomized withdrawal (RW) study (*Plazzi et al 2018*). The study enrolled 106 pediatric patients 7 to 17 years of age with a baseline history of ≥ 14 cataplexy attacks in a typical 2-week period prior to any treatment for narcolepsy symptoms. The primary endpoint was change in weekly number of cataplexy attacks from the last 2 weeks of the stable-dose period (baseline) to the 2 weeks of the DB treatment period.
  - Ninety-six (92%) patients completed the stable-dose period, of whom 63 (the efficacy population) were randomly assigned to receive sodium oxybate (n = 31) or placebo (n = 32) for 2 weeks. A preplanned interim analysis of the primary endpoint showed efficacy (p = 0.0002), resulting in discontinuation of the placebo arm following guidance from the data safety monitoring board; 33 patients then received sodium oxybate on an OL basis during the DB period. Patients who were randomly assigned to receive placebo and who were withdrawn from sodium oxybate (32/63 [51%]) had increased weekly cataplexy attacks (median increase of 12.7 attacks per week [first quartile {Q1}, third quartile {Q3} = 3.4, 19.8]) when compared with those randomly assigned to continue treatment with sodium oxybate (median increase of 0.3 attacks per week [-1.0, 2.5]; p < 0.0001).
  - The median change from baseline in ESS-Child and Adolescent (CHAD) scores was greater in the placebo group (3.0 [Q1, Q3 = 1.0, 5.0]), indicating increased sleepiness, compared with the sodium oxybate group (0.0 [-1.0, 2.0]; p = 0.0004).
- The safety and efficacy of oxybate salts were evaluated in an unpublished Phase 3, DB, PC, RW, MC study in 201 adults with narcolepsy with cataplexy currently untreated or treated with or without anticataplectics (*Xywav dossier 2020)*. Enrollment criteria included a history of ≥ 14 cataplexy attacks in a typical 2-week period prior to receiving

any narcolepsy treatment. The study included a 12-week, OL, optimization and titration period to transition patients to oxybate salts; a 2-week stable-dose period; a 2-week DB, RW period; and a 2-week safety follow-up. During the withdrawal period, patients were randomized 1:1 to placebo or to continue oxybate salts. The primary endpoint was the change in the weekly number of cataplexy attacks from the time during the 2 weeks of the stable-dose period to the time during the 2 weeks of the DB, RW period, as determined from patients' daily diaries. The key secondary endpoint was the change in the ESS score from the end of the stable-dose period to the end of the DB, RW period.
    - Prior to randomization, the median (Q1, Q3) number of weekly cataplexy attacks did not differ in patients randomized to placebo (1.1 [0.0, 7.9]) vs those who continued oxybate salts (1.0 [0.0, 4.4]). During the DB, RW period, patients randomized to continue oxybate salts experienced no change (median [interquartile range {IQR}], mean [SD]) in the weekly frequency of cataplexy attacks, while patients randomized to discontinue oxybate salts and take placebo experienced an increase in cataplexy attacks (median [Q1, Q3]: 0.0 [-0.5, 1.7], mean [SD]: 0.12 [5.77] vs 2.4 [0.0,11.6], mean [SD]: 11.46 [24.75] respectively; treatment difference, $p < 0.0001$).
    - Prior to randomization, the median (Q1, Q3) ESS score did not differ in oxybate salts-treated patients who were randomized to placebo vs those who continued oxybate salts treatment (13.0 [9.0, 17.0] vs 14.0 [10.0, 19.0], respectively). At the end of the DB, RW period, the change in median (Q1, Q3) ESS score from baseline for patients randomized to placebo vs oxybate salts was 2.0 (0.0, 5.0) vs 0.0 (-1.0, 1.0), respectively.
  - Oxybate salts have not been specifically studied in a pediatric clinical trial. Use of oxybate salts in pediatric patients ≥ 7 years of age with narcolepsy is supported by evidence from an adequate and well-controlled study of sodium oxybate in pediatric patients 7 to 17 years of age (*Plazzi et al 2018*, see above), a study in adults showing a treatment effect of oxybate salts similar to that observed with sodium oxybate (see above), pharmacokinetic (PK) data of sodium oxybate from adult and pediatric patients, and PK data of oxybate salts from healthy adult volunteers (*Xywav dossier 2020*).
- Solriamfetol:
  - The approval of solriamfetol was based on data from the Treatment of Obstructive sleep apnea and Narcolepsy Excessive Sleepiness (TONES) Phase 3 clinical program, which included 4 PC RCTs.
  - TONES 2 was a12-week, Phase 3, DB, PC, MC RCT (N = 239) that evaluated the safety and efficacy of solriamfetol in the treatment of type 1 or type 2 narcolepsy (*Thorpy et al 2019*). Patients were randomized to solriamfetol 75, 150, or 300 mg once daily. The co-primary endpoints were change from baseline to week 12 in mean sleep latency assessed by the MWT and ESS score. Improvement on the PGI-C was the key secondary endpoint.
    - Statistical significance was met for the co-primary endpoints and the PGI-C for the 150 and 300 mg doses, but not the 75 mg dose. At week 12, the least squares (LS) mean change from baseline on the MWT showed an increase in sleep latency of 12.3 and 9.8 minutes for 150 and 300 mg, respectively vs 2.1 minutes with placebo ($p < 0.0001$) (LS mean differences vs placebo: 10.1 [95% CI, 6.4 to 13.9] and 7.7 [95% CI, 4.0 to 11.3]). For the ESS score, the LS mean change from baseline at week 12 was -6.4, -5.4, and -3.8 for the 300 mg, 150 mg, and 75 mg doses of solriamfetol, respectively, and -1.6 with placebo (LS mean differences vs placebo: -4.7 [95% CI, -6.6 to -2.9]; $p < 0.0001$, -3.8 [95% CI, -5.6 to -2.0]; $p< 0.0001$, and -2.2 [95% CI, -4.0 to -0.3]; $p = 0.0211$). At week 12, higher percentages of patients treated with solriamfetol 150 mg (78.2%) and 300 mg (84.7%) reported PGI-C improvement vs placebo (39.7%; both $p < 0.0001$).
  - TONES 3 was a 12-week, Phase 3, DB, PC, MC RCT (N = 476) that evaluated the safety and efficacy of solriamfetol for the treatment of EDS in patients with OSA with current or prior sleep apnea treatment (*Schweitzer et al 2019*). Patients were randomized to solriamfetol 37.5, 75, 150, or 300 mg once daily. The co-primary endpoints were change from baseline to week 12 in mean sleep latency assessed by the MWT and ESS score. Improvement on the PGI-C was the key secondary endpoint.
    - The co-primary endpoints of change from baseline at week 12 in MWT and ESS were met at all solriamfetol doses, and the key secondary endpoint of PGI-C was met at all doses except the 37.5 mg dose. At week 12, the LS mean differences from placebo for solriamfetol 300, 150, 75, and 37.5 mg were 12.8 [95% CI, 10 to 15.6], 10.7 [95% CI, 8.1 to 13.4], 8.9 [95% CI, 5.6 to 12.1], and 4.5 [95% CI, 1.2 to 7.9] minutes, respectively ($p < 0.0001$ for 300, 150, and 75 mg; $p = 0.085$ for 37.5 mg). For the ESS score, the LS mean differences from placebo were -4.7 [95% CI, -5.9 to -3.4], -4.5 [95% CI,-5.7 to -3.2], -1.7 [95% CI, -3.2 to -0.2], and -1.9 [95% CI, -3.4 to -0.3], respectively ($p < 0.0001$ for 300 and 150 mg; $p = 0.0233$ for 75 mg; $p = 0.061$ for 37.5 mg). At week 12, higher percentages of patients on solriamfetol 75 mg (72.4%; $p < 0.05$), 150 mg (89.7%; $p < 0.0001$), and 300 mg (88.7%; $p < 0.0001$) reported overall improvement on the PGI-C vs placebo (49.1%).
  - TONES 4 was a Phase 3, DB, PC, MC RW study that evaluated the maintenance of efficacy and safety of solriamfetol vs placebo for the treatment of EDS in adults with OSA (*Strollo et al 2019*). After 2 weeks of clinical titration (n = 174, 75 mg once daily starting dose, titrated up or down every 3 days to 75, 150, or 300 mg) and 2 weeks of stable dose administration (n = 148), patients who reported much or very much improvement on the PGI-C and had numerical improvements on the MWT and ESS were randomly assigned to placebo or solriamfetol for 2 additional weeks.

- From baseline to week 4, mean MWT sleep latencies improved from 12.3 to 13.1 minutes to 29.0 to 31.7 minutes, and ESS scores improved from 15.3 to 16.0 to 5.9 to 6.4. Patient-reported EDS decreased from ~15 to 16 to ~6, which is within the normal range. From weeks 4 to 6 (RW phase), solriamfetol-treated patients maintained improvements in MWT and ESS. The LS mean change in MWT mean sleep latency was -12.1 minutes with placebo compared with -1.0 minute with solriamfetol; LS mean difference between solriamfetol and placebo was 11.2 minutes (95% CI, 7.8 to14.6; p < 0.0001). The LS mean changes in ESS scores were 4.5 and -0.1 for placebo and solriamfetol, respectively, resulting in an LS mean difference of -4.6 (95% CI, -6.4 to -2.8; p < 0.0001). During the RW phase, a statistically significant 50.0% of patients who were switched to placebo reported worsening on the PGI-C relative to 20.0% who continued using solriamfetol (-30.0; 95% CI, -46.0 to -14.0; p < 0.001). Similarly, 59.0% of patients switched to placebo worsened, as rated by the physicians on the CGI-C, vs 21.7% who continued using solriamfetol (-37.3; 95% CI, -53.50 to -21.19; p < 0.0001).

- TONES 5 was a Phase 3 OL extension study that evaluated the long-term safety and maintenance of efficacy of solriamfetol for up to 52 weeks in the treatment of patients with narcolepsy or OSA who completed previous trials of solriamfetol (*Malhotra et al 2019*, *Sunosi dossier 2019*). In a 2-week OL titration phase, patients were initiated on solriamfetol 75 mg, titrated to a maximum tolerated dose of 150 or 300 mg, followed by a maintenance phase. During a 2-week PC RW phase ~ 6 months later, patients were randomized either to placebo or to continue solriamfetol at their dose of 75 mg, 150 mg, or 300 mg for 2 weeks. The primary endpoint was change in ESS score during the RW phase.
  - The LS mean change from the beginning to the end of the RW phase for the ESS score was 1.6 with solriamfetol compared with 5.3 with placebo, resulting in an LS mean difference of -3.7 (95% CI, -4.80 to -2.65; p < 0.0001). Similar results were seen in the subgroup analysis of patients with OSA and patients with narcolepsy. The percentage of patients who were reported as worse on the PGI-C at the end of the RW phase was 64.5% for patients randomized to placebo compared to 28.2% for patients on solriamfetol (p < 0.0001). Long-term maintenance of efficacy of solriamfetol was demonstrated by sustained reductions in ESS scores in Group A (12-week narcolepsy or OSA study) for up to 40 weeks and in Group B (Phase 2 studies or 6-week Phase 3 study) for up to 52 weeks. During the RW period, patients did not demonstrate rebound sleepiness or withdrawal after abrupt discontinuation of solriamfetol.

Place in Therapy

- Narcolepsy:
  - The 2007 American Academy of Sleep Medicine (AASM) practice parameters for the treatment of narcolepsy and other hypersomnias of central origin (*Morgenthaler et al 2007a*) recommend pharmacologic therapy based on the diagnosis and targeted symptoms. Most of the agents used to treat EDS have little effect on cataplexy or other REM sleep associated symptoms, while most antidepressants and anticataplectics have little effect on alertness; however, some medications act on both symptoms. Co-administration of 2 or more drug classes may be required in some patients to adequately address their symptoms. Scheduled naps may be beneficial, but seldom suffice as primary therapy for narcolepsy. The guidelines state that modafinil is effective for treatment of EDS due to narcolepsy and sodium oxybate is effective for treatment of cataplexy, EDS, and disrupted sleep due to narcolepsy. Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis. Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of EDS due to narcolepsy. Antidepressants (TCAs, selective serotonin reuptake inhibitors [SSRIs], venlafaxine) may be effective for treatment of cataplexy. TCAs, SSRIs, and venlafaxine may be effective treatment for sleep paralysis and hypnagogic hallucinations.
  - The European Academy of Neurology (EAN) 2011 guidelines on management of narcolepsy in adults (*Billiard et al 2011*) recommend modafinil as the first-line treatment for EDS associated with narcolepsy when EDS is the most disturbing symptom. Sodium oxybate is recommended when EDS, cataplexy, and poor sleep coexist. The guideline notes that the combination of modafinil and sodium oxybate may be more effective than sodium oxybate alone. Methylphenidate may be an option if the response to modafinil is inadequate; sodium oxybate is not recommended. Naps are best scheduled on a patient-by-patient basis.
  - While armodafinil has been shown in clinical studies to be effective for EDS in narcolepsy, its specific place in therapy is not discussed in the current guidelines.
- OSA:
  - The 2006 AASM practice parameters for the medical therapy of OSA (*Morgenthaler et al 2006*) provide recommendations for patients with OSA who do not adapt well to or respond to initial therapy with CPAP, oral appliances, or surgical modification. Dietary weight loss in obese individuals may be beneficial and should be combined with a primary treatment for OSA. Modafinil is recommended for the treatment of residual EDS in OSA patients who have sleepiness despite effective PAP treatment and who are lacking any other identifiable cause for their sleepiness.
- SWD:

- The AASM practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders (*Morgenthaler et al 2007b*) recommend planned napping before or during the night shift to improve alertness and performance in patients with SWD. Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work. Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers. Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered. Modafinil is indicated to enhance alertness during the night shift for SWD. Caffeine is indicated to enhance alertness during the night shift for SWD.

Safety

- Modafinil/armodafinil:
  - Warnings and precautions of modafinil/armodafinil include rare serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); drug rash with eosinophilia and systemic symptoms (DRESS); multiorgan hypersensitivity; angioedema and anaphylaxis reactions; persistent sleepiness; psychiatric AEs; and CV AEs including chest pain, palpitations, dyspnea, and transient ischemic T-wave changes on electrocardiogram (ECG) in association with mitral valve prolapse or left ventricular hypertrophy. Increased monitoring of heart rate and blood pressure (BP) may be appropriate in patients receiving modafinil/armodafinil. Caution should be exercised when these drugs are prescribed to patients with known CV disease.
  - The most common AEs (≥ 5%) with armodafinil vs placebo were headache (17 vs 9%), nausea (7 vs 3%), dizziness (5 vs 2%), and insomnia (5 vs 1%).
  - The most common AEs (≥ 5%) with modafinil vs placebo were headache (34 vs 23%), nausea (11 vs 3%), nervousness (7 vs 3%), rhinitis (7 vs 6%), diarrhea (6 vs 5%), back pain (6 vs 5%), anxiety (5 vs 1%), insomnia (5 vs 1%), dizziness (5 vs 4%), and dyspepsia (5 vs 4%).
- Pitolisant:
  - Pitolisant is contraindicated in patients with severe hepatic impairment and has not been studied in these patients. Pitolisant is extensively metabolized by the liver and there is a significant increase in pitolisant exposure in patients with moderate hepatic impairment.
  - Pitolisant has a warning for QT prolongation. Use should be avoided with other drugs known to prolong the QT interval. Pitolisant should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval. Patients with hepatic or renal impairment should be monitored for increased QTc.
  - In the PC trials, the most common AEs (occurring in ≥ 5% of patients and at twice the rate of placebo) with the use of pitolisant were insomnia (6%), nausea (6%), and anxiety (5%).
- Solriamfetol:
  - Solriamfetol is contraindicated with concomitant use of monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of an MAOI because of the risk of hypertensive reaction.
  - Warnings and precautions of solriamfetol include BP and heart rate increases and psychiatric symptoms such as anxiety, insomnia, and irritability.
  - The most common AEs (≥ 5% and greater than placebo) in either the narcolepsy or OSA populations vs placebo were headache (16 vs 7%), nausea (7 vs 4%), decreased appetite (9 vs 1%), insomnia (5 vs 4%), and anxiety (6 vs 1%).
- Sodium oxybate/oxybate salts:
  - Sodium oxybate/oxybate salts are contraindicated in combination with sedative hypnotics or alcohol and in patients with succinic semialdehyde dehydrogenase deficiency, a rare inborn error of metabolism.
  - Sodium oxybate/oxybate salts carries a boxed warning concerning CNS depression and the potential for misuse/abuse. Abuse or misuse of illicit GHB is associated with CNS AEs, including seizure, respiratory depression, decreased consciousness, coma, and death.
  - Because of the risks of CNS depression and abuse and misuse, sodium oxybate/oxybate salts are available only through a restricted distribution program under a risk evaluation and mitigation strategies (REMS). Prescribers must be specially certified, and the drug may be dispensed only by a central pharmacy that is specially certified.
  - Other warnings and precautions include respiratory depression and sleep disordered breathing; depression and suicidality; parasomnias; and use in patients sensitive to high sodium intake due to the high salt content (sodium oxybate only).
  - The most common AEs with sodium oxybate in adults (≥ 5% and at least twice the incidence with placebo) were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.
  - The most common AEs with oxybate salts in adults (≥ 5%) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting.

- The most common AEs in pediatric patients in the oxybate salts RW trial (≥ 5%) were enuresis, nausea, headache, vomiting, weight decreased, decreased appetite, and dizziness.

Dosing

- Armodafinil:
  - Narcolepsy/OSA: 150 mg to 250 mg orally once daily in the morning
    - OSA: up to 250 mg once daily has been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond the 150 mg dose
  - SWD: 150 mg orally once daily approximately 1 hour prior to the start of the work shift
  - Hepatic impairment: dose should be reduced in patients with severe hepatic impairment
- Modafinil:
  - Narcolepsy/OSA: 200 mg orally once daily in the morning
  - SWD: up to 400 mg once daily has been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond the 200 mg/day dose
  - Hepatic impairment: dose should be reduced to one-half in patients with severe hepatic impairment
- Pitolisant:
  - Recommended dosage range: 17.8 mg to 35.6 mg per day administered once daily upon awakening.
    - Dose titration as follows:
      - Starting dose: 8.9 mg (two 4.45 mg tablets) once daily
      - Increase dose to 17.8 mg (one 17.8 mg tablet) once daily
      - May increase to a maximum of 35.6 mg (two 17.8 mg tablets) once daily
      - Dose may be adjusted based on tolerability
      - It may take up to 8 weeks for some patients to achieve a clinical response
  - Hepatic and renal impairment: dose adjustments recommended in hepatic and renal impairment; not recommended in patients with end-stage renal disease (ESRD)
    - Moderate hepatic impairment: 8.9 mg once daily, increased after 14 days to a maximum dosage of 17.8 mg once daily.
    - Moderate and severe renal impairment: 8.9 mg once daily, increased after 7 days to a maximum dosage of 17.8 mg once daily.
  - Poor cytochrome P450 (CYP) 2D6 metabolizers: dose should be initiated at 8.9 mg once daily and titrated to a maximum dose of 17.8 mg once daily after 7 days.
  - Co-administration with strong CYP2D6 inhibitors and strong CYP3A4 inducers: dose adjustments recommended (see prescribing information)
- Sodium oxybate/oxybate salts:
  - Adult dosing:
    - Starting dose: 4.5 g per night orally, divided into 2 doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later, increased by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dosage range of 6 to 9 g per night orally
  - Pediatric dosing:
    - Starting dose, titration regimen, and maximum dose: weight-based, administered twice nightly; titrated gradually based on efficacy and tolerability
  - Patients transitioning from sodium oxybate to oxybate salts should initiate therapy at the same dose and regimen as sodium oxybate (g for g).
  - Hepatic impairment: dose should be reduced to one-half of the original dosage per night, divided into 2 doses
  - Co-administration with divalproex sodium: dose of divalproex sodium should be reduced by ≥ 20% in patients already stabilized on sodium oxybate/oxybate salts; a lower starting dose should be used when introducing sodium oxybate/oxybate salts in patients already taking divalproex sodium.
- Solriamfetol:
  - Narcolepsy:
    - Starting dose: 75 mg once daily
    - Recommended dose range: 75 to 150 mg once daily, doubled at intervals ≥ 3 days based on efficacy and tolerability
    - Maximum recommended dose: 150 mg once daily
  - OSA:
    - Starting dose: 37.5 mg once daily
    - Recommended dose range: 37.5 to 150 mg once daily, doubled at intervals of ≥ 3 days based on efficacy and tolerability
    - Maximum recommended dose: 150 mg once daily
  - Renal impairment: dose adjustments required; not recommended in patients with ESRD

Conclusion

- Current treatment options for EDS in narcolepsy include modafinil, armodafinil, pitolisant, solriamfetol, sodium oxybate, oxybate salts, and amphetamine derivatives, thus providing several agents with differing mechanisms of action. Many patients with narcolepsy may require treatment with more than 1 drug class to manage co-existing symptoms. Pitolisant and sodium oxybate/oxybate salts are also FDA-approved for treatment of cataplexy in adults with narcolepsy. Antidepressants such as SSRIs or venlafaxine (used off-label) may be effective for treatment of cataplexy and provide a first- or second-line option. Modafinil, armodafinil, and solriamfetol are also indicated for EDS in patients with OSA, while modafinil and armodafinil are also indicated for SWD.
- Modafinil is generally considered the first-line pharmacologic therapy for narcolepsy. Its efficacy is well established and illicit use is uncommon. There are no apparent clinical advantages of the longer half-life enantiomer, armodafinil, over the racemic mixture, modafinil. These agents have not been compared head-to-head with CNS stimulants, such as dextroamphetamine or methylphenidate. Therapeutic benefits of modafinil and amphetamine derivatives become apparent within days. However, CNS stimulants have limited efficacy data, are associated with high abuse potential, and are associated with more AEs than modafinil/armodafinil. Modafinil/armodafinil may be beneficial for the treatment of OSA patients with residual EDS despite effective conventional treatment. Modafinil/armodafinil have warnings for rare serious skin reactions, angioedema/anaphylaxis, and multiorgan hypersensitivity; caution should be exercised in patients with known CV disease and increased monitoring of BP and heart rate may be appropriate for patients receiving these agents. Modafinil/armodafinil is a substrate, inducer, and inhibitor of CYP450 isoenzymes, resulting in the potential for drug interactions, including reduced efficacy of oral contraceptives. Modafinil/armodafinil have demonstrated variable efficacy for SWD in clinical trials and AEs may outweigh benefits in some patients.
- Pitolisant, a novel H_3 receptor antagonist/inverse agonist, was FDA-approved in August 2019 for the treatment of EDS in adults with narcolepsy and gained the expanded indication for treatment of cataplexy in adults with narcolepsy in October 2020. In two 8-week pivotal RCTs vs placebo and modafinil active control in patients with narcolepsy (a majority of whom had co-existing cataplexy), pitolisant appeared to have similar efficacy to modafinil for improving EDS. In HARMONY 1, a post-hoc analysis indicated that pitolisant reduced daily cataplexy episodes significantly more than placebo but not more than modafinil. In HARMONY 1bis, differences in WCR between pitolisant and placebo were not significant, nor were the differences between pitolisant and modafinil. In the HARMONY CTP trial in narcolepsy patients with severe cataplexy, pitolisant demonstrated a relative reduction in WCR of 75% vs 38% with placebo; improvements were also seen in ESS scores, MWT, and frequency of hallucinations. Differences in dosing titration and dosing ranges may have partially accounted for the lack of effect on cataplexy seen in HARMONY 1 and HARMONY 1bis as compared with HARMONY CTP. A dose-response analysis was not performed in these trials (*Wakix FDA clinical review 2019*).
  - Pitolisant requires a 3-week dose titration and may take up to 8 weeks to achieve a clinical response. Pitolisant does not appear to have significant abuse potential and is the only unscheduled narcolepsy agent. Pitolisant is generally well tolerated and has not been associated with CV AEs or vital sign changes; the most common AEs were headache, insomnia, and nausea. Although some patients in the pitolisant trials were receiving concomitant medication(s) targeting narcolepsy and/or cataplexy, trials specifically evaluating pitolisant in combination with other narcolepsy agents are lacking. Pitolisant is contraindicated in patients with severe hepatic impairment and has a warning for QT prolongation. Pitolisant is metabolized by CYP2D6 and CYP3A4 and has the potential for multiple drug interactions, including some antidepressants. Like modafinil/armodafinil, pitolisant may decrease the efficacy of oral contraceptives. Limited long-term safety and efficacy data are available, particularly at the highest recommended dose. A DB, PC RCT is currently ongoing to assess the safety and efficacy of pitolisant in children 6 to < 18 years of age with narcolepsy with or without cataplexy (*Clinicaltrials.gov Web site*).
- Sodium oxybate/oxybate salts have demonstrated efficacy in reducing EDS and cataplexy in patients with narcolepsy; however, use of these agents presents several challenges. Full therapeutic response may require several weeks to manifest and the dose must be titrated slowly; the split dosing regimen requires patients to wake during the night to administer a second dose. Use of sodium oxybate/oxybate salts is limited by abuse and drug diversion potential, CNS depression, and REMS requirement. Medications that suppress cataplexy often improve sleep paralysis and hypnagogic hallucinations, although these symptoms do not usually require pharmacologic therapy (*Scammell 2020b*). In narcolepsy patients with co-existing EDS, cataplexy, and disrupted nocturnal sleep, sodium oxybate/oxybate salts are the only agents that are effective for all 3 manifestations. They are also the only agents currently indicated for pediatric patients. Data have shown that the combination of modafinil and sodium oxybate may be more effective for the treatment of EDS than sodium oxybate alone. Oxybate salts may be preferred over sodium oxybate to lower daily sodium load in narcolepsy patients with comorbid conditions sensitive to salt intake, such as HTN, HF, or renal impairment.
- Solriamfetol demonstrated efficacy vs placebo for the treatment of EDS in narcolepsy and OSA in 4 RCTs and maintenance of efficacy in an OL extension trial of up to 52 weeks. The placebo subtracted change in sleep latency assessed by the MWT from baseline to end of treatment ranged from 10 to 13 minutes (out of a possible 40 minutes),

a statistically and clinically meaningful treatment effect. However, there are no head-to-head trials with other established narcolepsy agents. The onset of effect of solriamfetol became apparent within 1 week of initiation in clinical trials. Solriamfetol's main safety concern is the potential for BP and heart rate increases, which may be of particular concern in patients with narcolepsy or OSA who already often have CV risk factors such as HTN, diabetes, dyslipidemia, and obesity. In contrast to modafinil/armodafinil and pitolisant, solriamfetol lacks the concern for potential reduced efficacy of concomitant oral contraceptives.

BACKGROUND

Narcolepsy

- Narcolepsy is a rare chronic neurological disorder of hypersomnia that results from dysregulation of the sleep/wake cycle and intrusion of sleep into wakefulness. Its associated symptoms are potentially debilitating to patients.
- Narcolepsy results from the loss of the neuropeptides, orexin-A and orexin-B (also known as hypocretin-1 and hypocretin-2). These neurotransmitters are products of the prepro-orexin gene and are made by neurons in the lateral hypothalamus. Orexin-A and -B have excitatory effects when they bind the ox1 and ox2 receptors on postsynaptic neurons. The orexins are released during wakefulness and increase the activity of many brain regions involved in the promotion of wakefulness, including the locus coeruleus, raphe nuclei, and tuberomammillary nucleus. By increasing the activity of these wake-promoting aminergic neurons, orexins stabilize wakefulness, prevent inappropriate transitions into REM or non-REM sleep, and inhibit REM sleep. Loss of orexins may allow REM sleep-related phenomena (eg, cataplexy, hypnagogic hallucinations, and sleep paralysis) to intrude into wakefulness (*Scammell 2019a*).
- Narcolepsy is typically classified as type 1 (narcolepsy with cataplexy, Na-1) or type 2 (narcolepsy without cataplexy, Na-2). Na-1 results from a loss of cerebrospinal fluid (CSF) orexin-A concentration, whereas Na-2 does not involve low levels of CSF orexin-A (*Bhattarai & Sumerall 2017, Scammell 2020a, Szabo et al 2019*). Na-1 is estimated to have a prevalence of 25 to 50 per 100,000 people. Narcolepsy typically begins in the teens and early twenties, but occasionally occurs as early as age 5 or after age 40. The prevalence of Na-2 is uncertain, as it is less well studied and more difficult to diagnose; however, it has been estimated as 20 to 34 per 100,000 people (*Scammel 2020a*). Males and females are equally affected (*Bhattarai & Sumerall 2017, Sunosi dossier 2019, Szabo et al 2019*).
- EDS is present in all patients with narcolepsy. EDS is characterized by chronic pervasive sleepiness and sleep attacks/inadvertent naps triggered by overwhelming urges to sleep (*Sunosi dossier 2019*). Other symptoms include cataplexy, hypnagogic hallucinations, and sleep paralysis; however, only about one-third of patients have all 4 symptoms (*Scammell 2020a*). A 2013 survey of narcolepsy patients indicated that EDS is the most disabling symptom experienced in their daily lives (*Sunosi FDA summary review*).
- EDS is not specific to narcolepsy and can be due to habitual loss of nighttime sleep, sleep fragmentation, a circadian sleep-wake disorder, a primary neurological disorder, or sedating drugs. In narcolepsy, sleepiness is characterized by a daily underlying irresistible drive for sleep that is associated with impaired cognitive ability, reduced psychosocial functioning and QoL that puts patients at risk of work-related, home, or automobile accidents (*Szabo et al 2019*).
- EDS is typically the first presenting symptom of narcolepsy. All patients with narcolepsy have chronic sleepiness, but they do not sleep more than healthy individuals during a 24-hour period (*Scammell 2020a*). EDS is routinely accompanied by sleep attacks, which are abrupt involuntary sleep episodes lasting from a few seconds to several minutes.
- Sleep paralysis has been described as the disturbing temporary inability to move voluntary muscles at sleep-wake transitions and usually occurs at the point of waking, although it may also occur just before falling asleep. Episodes of sleep paralysis can be frightening because the immobility may be accompanied by hypnopompic hallucinations or a sensation of suffocation (*Bhattarai & Sumerall 2017, Scammell 2020a*).
- Hypnagogic hallucinations are vivid, often frightening visual, tactile, or auditory hallucinations that occur while falling asleep. They probably result from a mixture of wakefulness and the dreaming of REM sleep (*Scammell 2019a*).
- Cataplexy is emotionally-induced transient muscle weakness that manifests as limb, head, or facial weakness. Episodes of cataplexy develop over several seconds and patients remain conscious regardless of the varying duration and severity that may occur. Severe episodes can result in bilateral weakness or paralysis, causing the patient to collapse (*Scammel 2020a, Szabo et al 2019*).
  - Up to 60% of patients with narcolepsy have cataplexy. Cataplexy is usually triggered by positive emotions such as laughing, joking, or excitement and less frequently by negative emotions such as anger or frustration.
- Many patients with narcolepsy fall asleep rapidly but have substantial fragmentation in nocturnal sleep. This sleep maintenance insomnia seems paradoxical in a disorder characterized by EDS, and it may reflect a low threshold to transition from sleep to wakefulness (*Bhattarai & Sumerall 2017, Scammell 2020a).*
- Non-pharmacologic interventions may be of benefit for patients with narcolepsy (*Scammell 2020b*).
  - Regular napping may be sufficient for occasional patients, but most require pharmacologic therapy to reduce sleepiness and cataplexy. One or 2 well-timed, 20-minute naps may improve sleepiness, though some patients may require long naps. Specifically, a short nap around 1:00 or 2:00 PM is often helpful as it can improve alertness for 1

to 3 hours, reducing the need for stimulants in the afternoon. If possible, a brief nap at work or school is often helpful. Medications that may worsen daytime sleepiness (eg, opiates, benzodiazepines, alcohol, antipsychotics) should be avoided. Other medications such as theophylline or excessive caffeine intake may worsen insomnia, contributing to daytime sleepiness. Prazosin and other α-1 antagonists can worsen cataplexy.
  - Patients with narcolepsy are at increased risk for psychiatric co-morbidities, particularly depression and anxiety; have higher than expected rates of hypertension; and increased rates of obesity and diabetes. Thus, psychosocial support and regular screening for depression, hypertension, and obesity are important for patients with narcolepsy.
- Pharmacological interventions are the most common approach for treating narcolepsy. Current medications have been developed to target symptoms; however, most patients do not experience complete resolution despite receiving optimal standard treatment (*Bhattarai & Sumerall 2017, Scammell 2020b).*
- The goal of pharmacologic therapy is to improve alertness and thus performance and safety of important tasks and activities like school or work (*Scammell 2020b*).
  - Many sleep disorders (eg, sleep apnea, periodic leg movements) can coexist with narcolepsy, thereby contributing to symptoms. Such disorders should be addressed before initiating narcolepsy-specific medications.
  - Most of the drugs available to treat narcolepsy target either EDS or cataplexy. Thus, many patients who have both symptoms require more than 1 drug to manage their disease.
  - Since all patients with narcolepsy have some degree of EDS, most require a wakefulness-promoting medication. These agents improve performance (measured by reaction time and simulated driving tasks), but their ability to maintain wakefulness rarely exceeds 70 to 80% of normal. Currently available agents include modafinil/armodafinil and CNS stimulants such as methylphenidate or amphetamines. All are effective; however, modafinil is usually used as first-line therapy since it has been studied in PC RCTs and is associated with fewer AEs than traditional stimulants.
  - About 30% of narcolepsy patients have cataplexy that is substantial enough to warrant treatment. A REM-suppressing medication such as venlafaxine, fluoxetine, atomoxetine (all off-label) may be chosen as first-line agent; sodium oxybate, the sodium salt of GHB, is usually reserved for second-line use in patients who do not respond to these medications. The full therapeutic effect of sodium oxybate may require several weeks of treatment, while the benefit of amphetamines and modafinil become apparent within a few days. AEs of sodium oxybate are more common than with other medications used to treat narcolepsy. Sodium oxybate has the potential for abuse and dependence and is only available through a REMS program.

<u>OSA</u>
- OSA is a chronic disorder that is characterized by obstructive apneas and hypopneas caused by repetitive collapse of the upper airway during sleep. The diagnosis should be considered whenever a patient presents with symptoms such as EDS, snoring, and choking or gasping during sleep, particularly in the presence of risk factors such as obesity, male gender, and advanced age (*Kline 2019*).
  - The most common symptoms of OSA are daytime sleepiness and nocturnal snoring or “choking.” Approximately 20% of patients with OSA have EDS (*Sunosi dossier 2019*).
  - Other symptoms and signs may be suggestive of OSA. For example, sleep maintenance insomnia with repetitive awakenings should prompt consideration of OSA. Some patients with OSA complain of insomnia rather than daytime sleepiness because they are unable to maintain sleep; this phenomenon may be more common in females.
  - Morning headaches are reported by 10 to 30% of patients with untreated OSA. They are usually bifrontal and squeezing in quality, with no associated nausea, photophobia, or phonophobia. They typically occur daily or most days of the week and may last for several hours after awakening in the morning. The cause of the headaches is not well established and may be multifactorial; proposed mechanisms include hypercapnia, vasodilation, increased intracranial pressure, and impaired sleep quality.
  - Other associated symptoms and historical features include the following:
    - Awakening with a sensation of choking, gasping, or smothering
    - Awakening with a dry mouth or sore throat
    - Moodiness or irritability
    - Lack of concentration
    - Memory impairment
    - Decreased libido and impotence
    - Nocturia
    - Awakening with angina pectoris
    - History of hypertension, CV disease, cerebrovascular disease, or renal disease
    - History of type 2 diabetes mellitus
    - Depression
    - Symptoms of fibromyalgia
    - Gastroesophageal reflux disease (GERD)

- History of polycystic ovary syndrome
- OSA is most common among males who are 18 to 60 years old, although it is also common at other ages and in women; the prevalence is similar in postmenopausal women and men.

- Untreated OSA has many potential adverse clinical consequences, including EDS, impaired daytime function, metabolic dysfunction, and an increased risk of CV disease and mortality (*Kryger 2020*).
  - The goals of OSA therapy are to resolve signs and symptoms of OSA, improve sleep quality, and normalize the apnea-hypopnea index (AHI) and oxyhemoglobin saturation level.
  - All patients diagnosed with OSA should be offered PAP as initial therapy.
    - CPAP involves maintenance of a positive pharyngeal transmural pressure so that the intraluminal pressure exceeds the surrounding pressure. CPAP also stabilizes the upper airway through increased end expiratory lung volume. As a result, respiratory events due to upper airway collapse (eg, apneas, hypopneas) are prevented.
  - In patients with mild to moderate OSA who prefer not to use PAP or who fail to respond to it, oral appliances are an alternative therapy that have been shown to improve signs and symptoms of OSA and may be better tolerated in some patients than PAP. Upper airway surgery may supersede oral appliances as alternative therapy in patients with severe, surgically correctable, obstructing lesions of the upper airway.
  - Behavior modification is indicated for all patients who have OSA and a modifiable risk factor. Overweight or obese patients should be encouraged to lose weight. Patients with positional OSA should change their sleep position accordingly. All patients should be advised that alcohol and certain common medications, such as benzodiazepines, may worsen their OSA.
  - A variety of pharmacologic agents have been evaluated in RCTs as potential primary therapy for the management of sleep-disordered breathing in OSA, with the goal of replacing more burdensome therapies such as PAP or oral appliances. However, no pharmacologic agent has proven to be sufficiently effective to warrant replacement of such therapies.
  - Residual sleepiness is reported by approximately 10 to 15% of patients with adequately treated OSA (*Pepin 2020*).
    - Modafinil or armodafinil may be beneficial as adjunctive therapy for EDS that persists despite documentation of adequate and successful conventional therapy. The efficacy of these agents, particularly modafinil, for treatment of residual sleepiness in patients with OSA has been demonstrated in multiple RCTs and meta-analyses (*Kryger 2020, Pepin 2020*).

SWD

- Individuals who work night shifts commonly experience difficulties with both sleep and alertness at desired times, and shift work is increasingly recognized as a risk factor for a variety of adverse health outcomes including diabetes, cancer, and CV disease. While some shift workers show circadian adjustment to their work schedule, many others do not (*Cheng & Drake 2019*).
  - Those who do not adjust commonly experience excessive sleepiness during work and significant sleep disturbance. It is estimated that one-third or more of shift workers experience impairments of sufficient severity to meet formal criteria for SWD (ie, development of sleep disturbances and impairment of waking alertness and performance) (*Morgenthaler et al 2007b*).
  - Both sleep duration and sleep quality are commonly affected in shift workers. Shift workers generally report 30 to 60 minutes less sleep compared with day workers, and individuals with SWD report even greater reductions in sleep, with an average decrease of approximately 90 minutes.
  - Shift workers commonly report difficulty with sleep initiation and maintenance. Disturbances during wakefulness include excessive sleepiness, impaired cognitive function, decreased psychomotor functioning, and altered social and emotional functioning.
- Minimum measures to improve sleep after a night shift include a regular sleep schedule (ie, “anchor sleep”), light-blocking shades, and ambient noise control. If family or social responsibilities prohibit one 7- to 9-hour sleep period, a regularized 3- to 4-hour morning "anchor" sleep with a second variably timed sleep period is recommended (*Cheng & Drake 2019*).
- For patients with persistent difficulties obtaining adequate sleep despite sleep hygiene measures, options include use of a short-acting hypnotic agent, exogenous melatonin, and behavioral treatment of insomnia (sleep scheduling and cognitive-behavioral therapy). The choice among these depends on availability and cost, presence of contraindications, and patient preference (*Cheng & Drake 2019*).
  - Modafinil and armodafinil are options in patients with persistent sleepiness in conjunction with nonpharmacologic measures to improve sleep and alertness. The magnitude of benefit may vary among individuals. The observed benefits in RCTs have been modest, however, and AEs may outweigh benefits in some patients.

INDICATIONS

Table 1. FDA-approved indications for narcolepsy agents

Indication	armodafinil	modafinil	pitolisant	sodium oxybate/oxybate salts	solriamfetol
Narcolepsy	√	√	√	√	√
Narcolepsy-cataplexy			√	√	
OSA	√	√			√
SWD	√	√			

- Armodafinil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or SWD.
  - Limitations of Use
    - In OSA, armodafinil is indicated to treat excessive sleepiness and not as treatment for the underlying obstruction. If CPAP is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating and during treatment with armodafinil for excessive sleepiness.
- Modafinil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or SWD.
  - Limitations of Use
    - In OSA, modafinil is indicated to treat excessive sleepiness and not as treatment for the underlying obstruction. If CPAP is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating and during treatment with modafinil for excessive sleepiness.
- Pitolisant is indicated for the treatment of EDS or cataplexy in adult patients with narcolepsy.
- Sodium oxybate/oxybate salts are indicated for the treatment of cataplexy or EDS in patients ≥ 7 years of age with narcolepsy.
- Solriamfetol is indicated to improve wakefulness in adult patients with EDS associated with narcolepsy or OSA.
  - Limitations of Use
    - Solriamfetol is not indicated to treat the underlying airway obstruction in OSA. Ensure that the underlying airway obstruction is treated (eg, with CPAP) for at least 1 month prior to initiating solriamfetol for EDS. Modalities to treat the underlying airway obstruction should be continued during treatment with solriamfetol. Solriamfetol is not a substitute for these modalities.
- Off-label Uses (*Micromedex 2020; Class IIb or higher recommendation; evidence favors efficacy*) (see Appendix J for description of recommendation, efficacy, and evidence ratings)
  - Armodafinil
    - Bipolar disorder, depressed phase, in combination with conventional medications (Class IIb; Category B)
  - Modafinil
    - Attention deficit hyperactivity disorder (adult and pediatric) (Class IIb, Category B [adult]; Category A [pediatric]
    - Depression, unipolar or bipolar (Class IIb; Category B)
    - Depression; adjunct – fatigue (Class IIb; Category B)
    - Sleep deprivation (Class IIa; Category A)
    - Steinert myotonic dystrophy syndrome (Class IIb; Category B)
  - Sodium oxybate
    - Fibromyalgia (Class IIb; Category B)

PHARMACOLOGY

- Modafinil/armodafinil
  - The mechanism(s) through which armodafinil/modafinil promotes wakefulness is unknown. Armodafinil (R-modafinil) has pharmacological properties similar to those of modafinil (a mixture of R- and S-modafinil), to the extent tested in animal and *in vitro* studies. The R- and S-enantiomers have similar pharmacological actions in animals.
  - Armodafinil and modafinil have wake-promoting actions similar to sympathomimetic agents including amphetamine and methylphenidate, although their pharmacologic profile is not identical to that of the sympathomimetic amines.
  - Modafinil-induced wakefulness can be attenuated by the α1-adrenergic receptor antagonist, prazosin; however, modafinil is inactive in other *in vitro* assay systems known to be responsive to α-adrenergic agonists such as the rat vas deferens preparation.
  - Armodafinil is an indirect dopamine receptor agonist. Modafinil is not a direct- or indirect-acting dopamine receptor agonist. Both armodafinil and modafinil bind *in vitro* to the dopamine transporter and inhibit dopamine reuptake. For modafinil, this activity has been associated *in vivo* with increased extracellular dopamine levels in some brain regions of animals. In genetically engineered mice lacking the dopamine transporter (DAT), modafinil lacked wake-promoting activity, suggesting that this activity was DAT-dependent. However, the wake-promoting effects of modafinil, unlike those of amphetamine, were not antagonized by the dopamine receptor antagonist haloperidol in

rats. In addition, α-methyl-p-tyrosine, a dopamine synthesis inhibitor, blocks the action of amphetamine, but does not block locomotor activity induced by modafinil.
  - In the cat, equal wakefulness-promoting doses of methylphenidate and amphetamine increased neuronal activation throughout the brain. Modafinil at an equivalent wakefulness-promoting dose selectively and prominently increased neuronal activation in more discrete regions of the brain. The relationship of this finding in cats to the effects of modafinil in humans is unknown.
  - In addition to its wake-promoting effects and ability to increase locomotor activity in animals, modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants in humans. Modafinil has reinforcing properties, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine; modafinil was also partially discriminated as stimulant-like.
  - Based on nonclinical studies, 2 major metabolites, acid and sulfone, of modafinil or armodafinil, do not appear to contribute to the CNS-activating properties of the parent compounds.
- Pitolisant:
  - The mechanism of action of pitolisant in EDS in adult patients with narcolepsy is unclear. However, its efficacy could be mediated through its activity as an antagonist/inverse agonist at H_3 receptors.
- Sodium oxybate/oxybate salts
  - Sodium oxybate is a CNS depressant. The mechanism of action of sodium oxybate in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of GHB, an endogenous compound and metabolite of the neurotransmitter GABA. Oxybate salts is a mixture of calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate. It is hypothesized that the therapeutic effects of sodium oxybate and oxybate salts on cataplexy and EDS are mediated through GABA actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.
- Solriamfetol
  - The mechanism of action of solriamfetol to improve wakefulness in patients with EDS associated with narcolepsy or OSA is unclear. However, its efficacy could be mediated through its activity as a DNRI (*Sunosi prescribing information 2019*). Solriamfetol does not release norepinephrine, differentiating it from the noradrenergic-releasing effects of amphetamines (*Sunosi dossier 2019*).

CLINICAL EFFICACY

STUDY DESIGN ABBREVIATIONS: AC = active control; CI = confidence interval, DB = double-blind; HR = hazard ratio; MC = multi-center; OL = open-label; OR = odds ratio; PC = placebo-controlled; PG = parallel-group; RCT = randomized controlled trial; RR = relative risk; SB = single-blind; SC = single-center; XO = crossover

***Search Strategy**: Studies supporting the FDA-approved indications were identified using search terms "solriamfetol," "armodafinil," "modafinil," "sodium oxybate," "oxybate salts," "pitolisant," "obstructive sleep apnea," "cataplexy," "narcolepsy," and "shift work sleep disorder" through October 14, 2020. Manufacturer submitted data were also reviewed when available. A comprehensive PubMed literature search was performed for human studies published in English. Assessment of each study's design (eg, randomization, blinding methodology, appropriateness of treatment outcomes, etc.), validity and importance was completed. Review of patient data in groups to which they were randomized (intention to treat analysis), accounting for patient withdrawals, and baseline characteristics was completed.*

Modafinil/armodafinil

Narcolepsy

Study 1. Harsh et al, *Curr Med Res Opin.* 2006;22(4):761-774

Study Objective: Evaluate the efficacy and safety of armodafinil for the treatment of EDS in patients with narcolepsy	
Study Design, Follow-up	**Treatment Groups** (N = 196)
• 12-week, Phase 3, DB, PC, PG, MC, RCT	• Armodafinil 150 mg once daily (n = 64) • Armodafinil 250 mg once daily (n = 67) • Placebo (n = 63) • Study medication was administered before 8:00 AM (~30 min before breakfast) throughout the study. • Armodafinil was initiated at a dose of 50 mg/day in all patients; doses were increased to 100 mg/day on day 2 and titrated upward in 50 mg increments every 2 days until the final dose was achieved.
Inclusion Criteria	**Exclusion Criteria**

• Age 18 to 65 years • Diagnosis of narcolepsy according to the International Classification of Sleep Disorders (ICSD) criteria • No medical or psychiatric disorders other than narcolepsy that could have caused EDS • Mean sleep latency ≤ 6 min on the MSLT (Appendix B) and a Clinical Global Impression of Severity (CGI-S) rating ≥ 4 (moderately ill)	• Clinically significant uncontrolled medical or psychiatric illnesses (treated or untreated) • Probable diagnosis of a current sleep disorder other than narcolepsy in the opinion of the investigator • Consumption of > 600 mg/day of caffeine • History of alcohol, narcotic, or other drug abuse • Any disorder that might interfere with drug absorption, distribution, metabolism, or excretion • Use of disallowed drugs (modafinil, melatonin, sodium oxybate, lithium, St. John's Wort, methylphenidate, amphetamines, pemoline, antipsychotic agents, benzodiazepines, zolpidem, MAOIs, anticoagulants, anticonvulsants, barbiturates) • Use of clinically significant amounts of nonprescription drugs within 7 days of the screening visit • Use of anticataplectic drugs (ie, clomipramine, SSRIs, venlafaxine), other than sodium oxybate, were permitted if they did not contribute to patients' sleepiness and if doses were stable for at least 1 month prior to baseline
Co-primary Endpoints	**Secondary Endpoints**
• Change from baseline in mean sleep latency on the MWT 9:00 AM to 3:00 PM (Appendix C) • Proportion of patients with at least minimal improvement on the CGI-C	• Mean changes from baseline in the MWT 3:00 PM to 7:00 PM mean sleep latency • Attention and memory as assessed by the Cognitive Drug Research (CDR) battery (average of first 4 test sessions at 9:30 AM, 11:30 AM, 1:30 PM, and 3:30 PM) • ESS scores (Appendix D) • CGI-C ratings • BFI (score for global fatigue and score for worst fatigue over the previous 24 hours; range 1 to 10; a score ≥ 7 indicates severe fatigue [*Mendoza et al 1999*]) • Data from diaries (sleepiness, mistakes/near misses/accidents, and caffeine use)

- **Results:**
  - At baseline, the placebo and armodafinil 150 mg and 250 mg groups were generally well matched, although patients in the armodafinil 250 mg group were significantly younger than patients in the other groups ($p < 0.05$).
  - At screening, CGI-S ratings were similar across groups, with the majority of patients having marked or severe illness (mean sleep latency < 3 min on the MSLT), and no differences were found between groups in MSLT. In the placebo group, 65% of patients had cataplexy vs 69% and 66% in the armodafinil 150 mg and 250 mg groups, respectively.
  - Study discontinuation rates were 25% (n = 16) in the armodafinil 150 mg group; 16% (n = 11) in the armodafinil 250 mg group; and 14% (n = 9) in the placebo group (18.4% total discontinuation rate).
  - At the final visit, mean MWT 9:00 AM to 3:00 PM sleep latency increased 1.3, 2.6, and 1.9 min from baseline in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.9 min from baseline in the placebo group. Treatment differences from placebo were 3.2, 4.5, and 3.8 min in the 150 mg, 250 mg, and armodafinil combined groups, respectively (all $p < 0.01$).
  - Mean MWT 3:00 PM to 7:00 PM sleep latency at the final visit increased 1.5, 1.6, and 1.6 min in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.2 min from baseline in the placebo group. Treatment differences relative to placebo were 2.7, 2.8, and 2.8 min, for the 150 mg, 250 mg, and armodafinil combined groups, respectively. The differences for the armodafinil combined group vs placebo and the 150 mg group vs placebo were significant ($p < 0.05$ for both comparisons). The armodafinil groups, individually and collectively, also had numerically longer mean MWT 3:00 PM to 7:00 PM sleep latencies when compared with placebo at weeks 4, 8, and 12. These differences did not achieve statistical significance.
  - The proportion of patients with at least minimal improvement in the CGI-C was significantly higher for the armodafinil 150 mg, 250 mg, and combined groups compared with placebo at all time points during the study ($p < 0.0001$ for both individual doses and the combined group vs placebo at final visit). The proportion of patients rated as minimally, much, and very much improved on the CGI-C from baseline to final visit was 21%, 33% and 16%, respectively, for armodafinil 150 mg; 20%, 35%, and 18%, respectively, for armodafinil 250 mg; 20%, 34%, and 17%, respectively, for the armodafinil combined group; and 17%, 12%, and 3%, respectively, for placebo.

- At final visit, power of attention was significantly improved in the armodafinil 150 mg/day and armodafinil combined groups compared with placebo ($p < 0.05$). Although there were numerical differences in favor of both armodafinil dose groups and the combined group compared with placebo at each visit, statistical significance was not observed until the final visit. Effects on mean continuity of attention were numerically improved for the armodafinil groups compared with placebo, but the difference did not achieve statistical significance. At final visit, armodafinil (both doses and the combined group) demonstrated significantly greater improvements in quality of episodic secondary memory relative to placebo ($p < 0.05$). Improvement was observed at the week 4 visit and was maintained throughout the study. Armodafinil 250 mg and the combined group demonstrated significantly greater improvement in speed of memory relative to placebo ($p < 0.05$) at final visit.
- Differences in the change from baseline on the ESS were statistically significant in favor of each armodafinil group compared with placebo at weeks 8 ($p < 0.01$ for all comparisons) and 12 ($p < 0.01$) and at final visit (mean ± SD change from baseline: 150 mg/day, -4.1 ± 5.13, $p = 0.0044$; 250 mg/day, -3.8 ± 4.73, $p = 0.0015$; combined group, -3.9 ± 4.91, $p = 0.0006$). At week 4, there was a statistically significant difference in favor of armodafinil 150 mg/day ($p = 0.0402$). In patients receiving armodafinil 250 mg/day, the difference was not statistically significant ($p = 0.0760$). At the final visit, 21% of patients in the armodafinil 150 mg/day group ($p = 0.0312$) and 28% of patients in the armodafinil 250 mg/day group ($p = 0.0023$) had an ESS score < 10, compared with only 7% of patients in the placebo group.
- Improvements on the BFI in the armodafinil 150 mg/day, 250 mg/day, and combined armodafinil group at final visit were statistically greater than placebo (mean change from baseline: 150 mg/day, -1.5 ± 2.14, $p = 0.0007$; 250 mg/day, -1.3 ± 2.09, $p = 0.0018$; combined group, -1.4 ± 2.11, $p = 0.0002$; placebo, -0.3 ± 1.89). There was a trend toward improvement from baseline in mean worst fatigue scores over the previous 24 hours at final visit, but the differences with armodafinil (all groups) vs placebo were not statistically significant ($p > 0.05$).
- Treatment with armodafinil 150 and 250 mg/day reduced the mean daily number of unintended sleep episodes by 33% and 44%, respectively, compared with a 10% reduction seen in the placebo group ($p < 0.0001$ for overall treatment comparison). The mean number of daily naps was reduced by 41%, 44%, and 22%, respectively, for the armodafinil 150 mg, armodafinil 250 mg, and placebo groups ($p = 0.0039$ for overall treatment comparison). The mean number of mistakes/near misses/accidents was reduced by 43% and 30% in the armodafinil 150 mg/day and 250 mg/day groups, respectively, compared with a 10% reduction in the placebo group. These differences, however, did not achieve statistical significance ($p = 0.1792$ for overall treatment comparison). Caffeine use, which was measured by the number of caffeinated drinks consumed each day, remained similar in the armodafinil and placebo groups (mean change from baseline, -0.7, -1.6, and 0.6 for armodafinil 150 mg, armodafinil 250 mg, and placebo, respectively).
- Headache, nausea, dizziness, and decreased appetite were the most commonly reported AEs. Most were considered mild to moderate, occurred with the greatest frequency during the first 2 weeks of therapy, and were self-limiting.
- There were no significant effects of armodafinil on nighttime sleep, including sleep initiation, continuity, or sleep stage variable as assessed by PSG. There was no change in the incidence of self-reported cataplexy.

- **Authors' conclusion:**
  - In patients with EDS associated with narcolepsy, armodafinil, at doses of 150 or 250 mg/day, significantly improved wakefulness throughout the day, clinician ratings of overall clinical condition, and some measures of memory and attention compared with placebo.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Cephalon
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Both objective and subjective measures were used to assess efficacy.
  - **Study limitations:**
    - The study was of short duration and did not provide information on the long-term efficacy and safety of armodafinil.
    - The study was not powered to detect differences between the 150 mg and 250 mg armodafinil doses. In addition, there was a significant difference in baseline MWT sleep latency between the 150 mg and 250 mg dose groups. Thus, additional research is needed to clarify the dose proportionality of armodafinil in the narcolepsy population.
    - The effect of armodafinil on memory processes requires further study.

Study 2. Golicki et al, *Med Sci Monit.* 2010;16(8):177-186

Study Objective: Evaluate the efficacy and safety of modafinil vs no active treatment or other drugs in the treatment of narcolepsy

Study Design, Follow-up	Treatment Groups
• Systematic review and meta-analysis (9 RCTs, N = 1054) • Three studies were SC; 4 were MC in 1 country and 2 were MC in more than 1 country. • Sample size varied between 10 and 283; however, only 3 studies included > 100 patients. • All studies were DB and 5 were XO.	• Modafinil any dose or regimen (n = 629) • Placebo or other active treatment (n = 425) • All studies compared modafinil with placebo and 1 also with sodium oxybate in patients with narcolepsy previously treated with modafinil in fixed doses for 4 weeks.
Inclusion Criteria	**Exclusion Criteria**
• Prospective, PG, or XO RCTs, SB or DB published as full text in peer reviewed journals • Study participants with adult (> 17 years old) narcolepsy with or without cataplexy	• Retrospective studies • Studies comparing different doses of modafinil • Secondary publication of an already included study
Primary Endpoints	**Secondary Endpoints**
• Elimination of EDS assessed by objective laboratory tests (MSLT, MWT) or validated subjective outcome measures (ESS) • Number and duration of severe somnolence, sleep attacks and naps, as reported by patients	• QoL assessed by validated generic questionnaires (SF-36) or validated sleep specific questionnaires • Disease severity assessed by the CGI-S • Performance assessed with the 4-choice reaction time test (FCRTT) • Steer Clear Performance Test (SCPT) • Physician evaluation of alerting effect on visual analog scale (VAS) • AEs • Withdrawals due to AEs

- **Results:**
  - Most of the included studies were of good quality and 1 was of poor quality. Five studies did not provide information on allocation concealment, and 4 had adequate allocation concealment. None of the studies reported proper intent-to treat (ITT) analysis; in 2 studies it was unclear and in 3 studies the authors provided analysis for all randomized patients who received study medication and had at least 1 post-baseline measure for efficacy (modified ITT [mITT]). Follow-up ranged from 2 to 9 weeks.
  - A fixed effect model was used by default, but if heterogeneity was detected, a random effects model was used.
  - Modafinil vs placebo:
    - The MSLT was used in 3 studies. In 2 PG studies, there was a greater increase in mean sleep latency with modafinil as compared with placebo: WMD 1.11 min (95% CI, 0.55 to 1.66); I^2 = 0%; test for overall effect: Z = 3.90 (p < 0.0001). The XO study presented median values, which were higher in the modafinil treatment phase compared with the placebo treatment phase (6.6 min vs 3.2 min; p < 0.05).
    - The MWT was used in 6 studies. In 4 PG studies and 2 XO studies, there was a greater increase in mean sleep latency with modafinil as compared with placebo: WMD 2.82 min (95% CI, 2.40 to 3.24); I^2 = 0%; test for overall effect: Z = 13.14 (p < 0.00001). There were similar increases in mean sleep latency in both the PG and XO studies.
    - The ESS scale was used in 6 studies. In 3 PG studies and 1 XO study, there was a greater reduction in the mean ESS score: WMD -2.73 points (95% CI, -3.39 to -2.08); I^2 = 0%; test for overall effect: Z = 8.17 (p < 0.00001). The ESS score was lower with modafinil vs placebo in both the XO and PG studies. In 1 XO study, the median ESS score decreased from 14.5 points during placebo treatment to 12.5 points after 3 weeks of modafinil treatment (p < 0.05). In another PG study which reported median values, no significant change in median average ESS score in the modafinil group was seen as compared with the placebo group (from 14 points to 15 points vs from 16 points to 16 points; p = 0.77).
    - Modafinil also improved the number (p = 0.006) and duration (p = 0.03) of severe somnolence episodes, sleep attacks, and naps per day as compared with placebo.
    - Elimination of cataplexy was assessed in 4 studies. There was no significant effect of modafinil as compared with placebo in 3 XO studies, as well as in 1 PG study: WMD 0.02 (95% CI, -0.27 to 0.31); I^2 = 71%; test for overall effect: Z = 0.13 (p = 0.90).
    - QoL was measured in 2 PG studies using the SF-36 and validated narcolepsy-specific questionnaire. At the end of a 9-week treatment period, patients receiving modafinil compared with those receiving placebo had significantly higher scores in 5 out of 7 narcolepsy-specific domains, SF-36 mental health summary scale and 4 (modafinil 200 mg/day) or 5 (modafinil 400 mg/day) SF-36 domains.

- CGI-S was assessed in 4 studies. In 1 XO study, CGI-S was non-significantly higher during the 4-week modafinil treatment period compared with the placebo phase (2.29 vs 2.0; p = 0.19). Two out of 3 PG studies showed significantly larger numbers of patients who improved according to physician assessment as compared with placebo groups. One study did not show a significant effect. The pooled effect estimate was significant (RR 1.6, 95% CI, 1.32 to 1.95); however, there was moderate heterogeneity (I^2 = 46%), introduced by Black and Houghton 2006 (see study 9 below), which enrolled patients already treated with modafinil and used different doses of the drug. Pooled CGI data from 2 studies showed significant improvement with no corresponding heterogeneity (RR 2.83, 95% CI, 1.90 to 4.20; I^2 = 0%).
- FCRTT was assessed in 3 studies. In 1 XO study, the modafinil treatment phase compared with the placebo treatment phase was associated with significant reductions in the number of gaps and the percentage of errors, and non-significant reduction in the mean reaction time. In another XO study and PG study, no significant difference between the modafinil and placebo groups were observed.
- SPCT was assessed in 2 studies. Significant improvement in driving ability was observed in the modafinil group as compared with the placebo group (WMD -2.54, 95% CI, -4.24 to -0.85).
- Physician evaluation of alerting effect on VAS scale was used in 1 XO study. No significant difference between the modafinil and placebo treatment phase was seen for alerting effect.

○ Modafinil vs sodium oxybate:
- No significant difference was observed between modafinil and sodium oxybate groups in the change of the mean sleep latency as measured by the MWT (MD -1.11 (95% CI, -3.02 to 0.8). The ESS score decreased in sodium oxybate group from 15 to 12 points and increased in modafinil group from 14 to 15 points (see study 9 below).

○ Safety:
- Modafinil was associated with more patient withdrawals from treatment due to AEs (4% vs 1.6% in placebo group); however, pooled RR was not significant: 2.06 (95% CI, 0.83 to 5.09); I^2 = 14%; test for overall effect: Z = 1.57 (p = 0.12).
- Significantly more patients reported nausea in the modafinil group as compared with placebo group. Other reported AE rates were similar between the groups.
- In the study comparing modafinil with sodium oxybate, non-significantly fewer patients in modafinil group compared to sodium oxybate group discontinued treatment due to AEs (3.2% vs 7.3%). Any AE rate was also similar in the modafinil and sodium oxybate groups (54% vs 60%). The most commonly reported AE was nausea, which was rare in the modafinil compared to the sodium oxybate group (3.2% vs 22%; RR 0.15, 95% CI, 0.03 to 0.62). Other AE rates were similar in modafinil and sodium oxybate groups.

• **Authors' conclusion:**
○ On the basis of 9 included studies, it can be concluded that in patients with narcolepsy modafinil in comparison with placebo was associated with significant benefit in terms of elimination of EDS assessed by objective laboratory tests or validated subjective outcome measures, but was not different from placebo in elimination of cataplexy as measured by the number of attacks per day. In addition, modafinil improved QoL of narcolepsy patients measured both by generic and a narcolepsy-specific questionnaire, and was associated with greater likelihood of improvement according to physician assessment.
○ On the basis of 1 study, it can be concluded that modafinil had a similar effect on EDS as sodium oxybate.
○ Modafinil has not been compared directly to methylphenidate, a common treatment of EDS, in any RCTs.

• **Study Appraisal:**
○ **Study sponsorship:**
- The review was partially based on Health Technology Assessment (HTA) report prepared by 2 of the authors to support Polish reimbursement application of modafinil manufactured by Torrex Chiesi. Both authors received grants from Torrex Chiesi Poland Sp.zo.o.

○ **Study rating:**
- N/A

○ **Study strengths:**
- The MA included a large number of RCTs, structured assessment of study quality, and pooled assessment of the modafinil treatment effect.

○ **Study limitations:**
- The length of follow-up of the included studies was short (2 to 9 weeks).
- Due to the small number of trials it was not possible to formally assess the presence of publication bias.
- More than half of the included studies were of XO design. Pooling of XO and PG group studies is considered controversial by some researchers. In this analysis, results of XO and PG studies were pooled separately in subgroups, and then all together.

Study 3. Mitler et al. *Sleep Med.* 2000;1(3):231-243

- A 40-week, OL extension study assessed the long-term efficacy and safety of modafinil in 478 patients with EDS associated with narcolepsy who completed 1 of the 2 pivotal 9-week RCTs of modafinil. A flexible-dose regimen (ie, 200, 300, or 400 mg daily) was followed in 1 study. In the second study, patients received 200 mg/day for 1 week, followed by 400 mg/day for 1 week. Investigators then prescribed either 200 or 400 mg doses for the duration of the study; the majority of patients (~75%) received 400 mg/day. The study was completed by 341 patients (71%).
  - At week 2, CGI-C scores indicated improvement in disease severity in 394/477 (83%) patients from OL baseline which was sustained through week 40. CGI-C scores indicated no change in disease severity in 7 ± 10% of patients and a worsening of symptoms in 9 ± 10% of patients. A total of 236 of 477 patients (49%) were considered much improved or very much improved at week 2. The percentage of patients considered to be much improved or very much improved increased significantly to 58, 59, and 58%, respectively, at weeks 8, 24, and 40 ($p < 0.001$ vs week 2 at all time points). The mean ESS score improved significantly from 16.5 at OL baseline to 12.4 at week 2 and remained at that level through week 40 ($p < 0.001$). QoL scores at weeks 4, 8, 24, and 40 were significantly improved vs OL baseline scores for 6 of the 8 SF-36 domains ($p < 0.001$).
  - The most common treatment-related AEs were headache (13%), nervousness (8%), and nausea (5%). Most AEs were mild to moderate in severity. Forty-three patients (9.0%) discontinued treatment because of AEs.
  - The authors concluded that modafinil was effective for the long-term treatment of EDS associated with narcolepsy and significantly improved perceptions of general health. Modafinil was well tolerated, with no evidence of tolerance developing during 40 weeks of treatment.

Study 4. Black et al. *J Clin Sleep Med.* 2010;6(5):458-66

- The long-term efficacy and safety of armodafinil in patients with EDS associated with treated OSA, SWD, or narcolepsy who completed one of four 12-week pivotal RCTs was assessed in a 12-month, flexible-dose (50 to 250 mg/day), OL extension study. Of 743 enrolled patients (474 with treated OSA, 113 with SWD, and 156 with narcolepsy), 57% of patients (420/743) completed 12 months or more of treatment.
  - Compared with baseline, minimal or greater improvement on the CGI-C was reported by most patients in the 3 diagnostic groups (75 to 92%) at final visit; patients in the SWD group reported the greatest improvement. A rating of much or very much improved was reported at the final visit by 65% (295/457) of patients with treated OSA (95% CI, 60.2 to 68.9), 88% (92/105) with SWD (95% CI, 81.3 to 93.9), and 62% (93/150) with narcolepsy (95% CI, 54.2 to 69.8). At baseline, the proportion of patients with a normal ESS score (ie, < 10) was 0.4% (2/454) in the treated OSA group and 3.4% (5/147) in the narcolepsy group. At the final visit, mean ESS score was reduced by 6.4 (95% CI,
    -6.90 to -5.94) in the treated OSA group and by 4.3 (95% CI, -5.20 to -3.49) in the narcolepsy group. The proportion of patients with an ESS score < 10 at final visit was 54.8% (249/454) for treated OSA and 31.3% (46/147) for narcolepsy. At final visit, mean global BFI scores were reduced by 1.7 (95% CI, -1.88 to -1.43) in the treated OSA group, 2.3 (95% CI, -2.75 to -1.87) in the SWD group, and 1.7 (95% CI, -2.13 to -1.35) in the narcolepsy group; mean worst fatigue scores were reduced by 1.8 (95% CI, -2.13 to -1.57) in the treated OSA group, 2.4 (95% CI, -3.06 to -1.83) in the SWD group, and 1.5 (95% CI, -2.00 to -1.07) in the narcolepsy group.
  - The most commonly reported AEs were headache (25% [180/731]), nasopharyngitis (17% [123/731]), insomnia (14% [99/731]), and upper respiratory tract infection (10% [76/731]). Most AEs were mild or moderate in intensity. Modest increases were observed in vital sign measurements (BP [3.6/2.3 mm Hg], heart rate [6.7 beats per min (bpm)]) across all patient groups; most of the changes occurred by month 3. Discontinuations due to AEs occurred in 13% of patients (95/743) during the 12-month period.
  - The authors concluded that armodafinil remained effective and was generally well tolerated. Increased monitoring of BP may be appropriate in patients on armodafinil. Armodafinil represents an option for long-term treatment of patients with EDS associated with treated OSA, SWD, or narcolepsy.

<u>OSA</u>

Study 5. Kuan et al, *Clin Ther.* 2016;38(4):874-888

Study Objective: Evaluate the efficacy of modafinil and armodafinil in treating EDS in patients with OSA	
Study Design, Follow-up	**Treatment Groups**
• Systematic review and meta-analysis (N = 11 modafinil RCTs and 5 armodafinil RCTs)	• Modafinil 200 to 400 mg daily x 1 to 12 weeks (N = 723) • Armodafinil 150 to 250 mg daily x 2 to 12 weeks (N = 1009) • Placebo • Sample sizes of the 16 RCTs ranged from 20 to 392.
Inclusion Criteria	**Exclusion Criteria**

• RCTs that: ○ Compared the outcomes of the use of placebo and either modafinil or armodafinil in patients with OSA ○ Described all inclusion and exclusion criteria used for patient selection ○ Reported doses and durations of study drugs	• Trials that included patients < 18 years of age or duplicate reports of patient cohorts
Primary Endpoints	**Secondary Endpoints**
• Sleep latency assessed by the MSLT or MWT • ESS • Karolinska Sleepiness Scale (KSS) (Appendix E) • Stanford Sleepiness Scale (SSS) (Appendix F)	• CGI-C • Patient-reported daily function assessed using the 10-item Functional Outcomes of Sleep Questionnaire (FOSQ-10), which measures functional status for disorders of EDS • Psychomotor Vigilance Tests

- **Results:**
  - Most trials investigated whether modafinil or armodafinil with concurrent CPAP use improved sleepiness, neurocognitive performance, and functional outcome in patients with sleep apnea. In 2 studies, CPAP was stopped during modafinil treatment. One study of modafinil and 1 study of armodafinil included untreated patients with OSA. Two studies of modafinil did not specify whether patients received CPAP.
  - Six studies reported acceptable methods of randomization and 6 studies described methods of allocation concealment. All studies reported patient blinding and the outcomes assessors used, and 1 trial reported the blinding of clinicians. Two studies used an ITT analysis without loss to follow-up. For all studies, the acceptable percentage of patients lost to follow-up was < 20%, except in 2 studies in which the levels were 20% and 21%.
  - A pooled estimate of the MDs in sleepiness parameters vs placebo were calculated using a random effects model.
  - Subjective sleepiness:
    - Subjective sleepiness in patients with OSA receiving CPAP was assessed using ESS in 5 RCTs of modafinil and 4 RCTs of armodafinil. Modafinil (WMD -2.95 [95%CI, -3.73 to -2.17]) and armodafinil (WMD -2.78 [95%CI, -3.51 to -2.05]) significantly improved subjective sleepiness compared with placebo ($I^2 = 0\%$).
    - Four studies evaluated the effects of modafinil on subjective sleepiness during acute CPAP withdrawal or in CPAP-naïve patients with OSA. There was a significant reduction in daytime sleepiness duration ($p < 0.05$) and significant improvements on the ESS ($p = 0.003$ [1 study]), KSS ($p = 0.04$ and $p = 0.01$ [2 studies]), SSS ($p = 0.03$ [1 study]), and daytime sleepiness VAS ($p = 0.01$ [1 study]). A non-significant trend of improved self-reported sleepiness on the ESS after armodafinil use among patients with OSA before CPAP treatment was observed in 1 study ($p = 0.066$).
  - Objective sleepiness:
    - Sleep latency with CPAP use was assessed using the MWT after modafinil treatment in 4 studies and after armodafinil treatment in 3 studies. Sleep latency was significantly prolonged in the modafinil group vs the placebo group (WMD 2.51 [95% CI, 1.5 to 3.52]) and armodafinil was associated with significant improvement vs placebo (WMD 2.71 [95% CI, 0.02 to 5.37]). However, a meta-analysis of data from 3 RCTs that compared the effects of modafinil and placebo on sleep latency, as assessed by the MSLT found no significant differences.
  - Overall clinical impression and daily functioning:
    - The proportion of patients with improvement on the CGI-C was evaluated in 3 RCTs of modafinil and 4 RCTs of armodafinil. There was significant improvement in both the modafinil and armodafinil groups vs the placebo group, with pooled RR of 1.94 (95% CI, 1.53 to 2.44) and 1.48 (95 % CI, 1.17 to 1.87), respectively.
    - The FOSQ was used in 4 RCTs that evaluated modafinil. Data were pooled on changes from baseline in total scores from 3 RCTs. In 1 study, the modafinil group showed significant improvement compared with placebo with an MD of 1.28 (95% CI, 0.64 to 1.91). The other 2 trials were not included because of incomplete data. One study found a non-significant trend toward improvement with modafinil in total FOSQ score ($p = 0.093$) and another study reported a non-significant trend in the vigilance subdomain of the FOSQ in the modafinil group ($p = 0.06$). One study reported that armodafinil treatment resulted in significant improvement in the subdomains of general productivity ($p = 0.01$) and social outcome ($p = 0.005$) compared with placebo. However, 2 RCTs conducted in an earlier period yielded divergent results regarding the effects of the medications.
  - Neurocognitive and driving performance:
    - Psychomotor vigilance tests indicated significant reductions in mean reaction time in 3 RCTs. Simulated driving performance was significantly improved in patients with OSA and acute CPAP withdrawal ($p = 0.018$) and in those awaiting CPAP initiation ($p < 0.0001$). One study reported a significant improvement in the composite Driving Safety Score ($p = 0.03$), assessed using the Cognitive Research Corporation Driving Simulator, in CPAP-naïve patients with OSA who received armodafinil compared with placebo.
  - AEs:

- Headache was the most commonly reported AE with both medications with RR of 1.78 (95% CI, 1.20 to 2.65) in the modafinil group and 2.04 (95% CI, 1.36 to 3.05) in the armodafinil group. Most AEs were generally of mild to moderate severity. Other AEs included nausea, anxiety or nervousness, insomnia, and dizziness.

- **Authors' conclusion:**
  - Modafinil or armodafinil treatment significantly improved sleepiness, clinical global impression, and total FOSQ scores in patients with OSA and excessive sleepiness with or without concurrent CPAP use. The results on neurocognitive performance were inconsistent. Most AEs were well tolerated.
- **Study Appraisal:**
  - **Study sponsorship:**
    - No funding was received from any industry or organization.
  - **Study rating:**
    - N/A
  - **Study strengths:**
    - Eligibility criteria were applied systematically and explicitly.
  - **Study limitations:**
    - The sample size of some of the included RCTs was small.
    - Most of the trials were short-term, with a maximum duration of 12 weeks.
    - Some numeric data analyzed statistically were estimated using graphics in the original publications because complete data were unavailable.
    - Concurrent use of CPAP was not consistent across all trials.
    - Patients were normotensive at baseline; thus, the study findings cannot be extrapolated to hypertensive patients.

SWD

Study 6. Czeisler et al. *Mayo Clin Proc*. 2009;84:958-972.

Study Objective: Evaluate the effect of armodafinil on the physiologic propensity for sleep and cognitive performance during usual night shift hours in patients with excessive sleepiness associated with chronic moderate to severe SWD	
Study Design, Follow-up	**Treatment Groups** (N = 254)
• 12-week, Phase 3, DB, PC, PG, MC, RCT • Patients were evaluated at weeks 4, 8, and 12 during an overnight laboratory night shift scheduled immediately after a sequence of ≥ 3 consecutive work night shifts.	• Armodafinil 150 mg 30 to 60 minutes before each night shift and no later than 11:00 PM (n = 127) • Placebo (n = 127) • Patients received a dose of 50 mg on the first night, 100 mg on the second and third nights, and 150 mg on all subsequent nights. Patients took study medication only on nights when they worked the night shift or attended the sleep laboratory.
Inclusion Criteria	**Exclusion Criteria**
• Age 18 to 65 years • Worked 5 or more night shifts per month (each shift ≤ 12 hours, with ≥ 6 hours worked between 10:00 PM and 8:00 AM and with ≥ 3 shifts occurring on consecutive nights) and planned to maintain this schedule for the duration of the treatment • Diagnosis of SWD according to the ICSD • SWD of moderate or greater severity, as documented by a CGI-S rating ≥ 4 for sleepiness on work nights, including the commute to and from work • Chronic (≥ 3 months) excessive sleepiness during night shifts, which was corroborated by a mean sleep latency of 6 minutes or less on a nighttime MSLT • Insomnia, as indicated by daytime sleep efficiency of 87.5% or less (determined by 8-hour PSG)	• History of substance abuse or medical or psychiatric disorders that could account for excessive sleepiness during the night shift • Any disorder that might interfere with drug PK • Known sensitivity to stimulants or modafinil • Consumption of an average of > 600 mg/day of caffeine during the 7 days preceding the baseline visit • Use of prescription drugs disallowed by the protocol or clinically important amounts of nonprescription drugs within 7 days of the screening visit
Primary Endpoints	**Secondary Endpoint**
• Change from baseline to final visit (12-week or last post-baseline measurement) in overall mean sleep	• Patient sleepiness assessed using the KSS

latency (averaged across the last 4 nighttime sessions at 2:00, 4:00, 6:00, and 8:00 AM) as assessed by the MSLT • Proportion of patients with at least minimal improvement in the CGI-C during the night shift and commute to and from work at the final visit (12-week or last post-baseline measurement)	• The CDR was administered at 12:30, 2:30, 4:30, 6:30, and 8:30 AM of each laboratory night shift. ○ The CDR battery included tests of memory (eg, numeric working memory test, word recognition test, immediate word recall test, delayed word recall test, and picture recognition test) and attention ○ Composite factors derived from the CDR included quality of episodic secondary memory (ability to encode, store, and retrieve verbal and pictorial information of an episodic nature), speed of memory (time required to retrieve information from episodic and working memory), power of attention (ability to focus attention), and continuity of attention (ability to sustain attention).

- **Results:**
  - Of the 254 patients randomized, 245 (96%) received at least 1 dose of study drug and 172 patients completed the study (84 placebo, 93 armodafinil).
  - The armodafinil and placebo groups were similar in baseline demographic variables and illness severity ratings. Overall, 138 (56%) of 245 patients were rated by the investigator as moderately ill, and 107 (44%) of 245 patients were rated as markedly, severely, or extremely ill. Most patients (212/245; 87%) were permanent night shift workers.
  - Sixty-eight (28%) of 245 patients withdrew from the study (30 in the armodafinil group and 38 in the placebo group). Reasons for discontinuing were AEs (7 in the armodafinil group and 4 in the placebo group), consent withdrawn (3 in the armodafinil group and 16 in the placebo group), loss to follow-up (3 in the armodafinil group and 5 in the placebo group), nonadherence with study procedures (6 in the armodafinil group and 2 in the placebo group), and other (11 in the armodafinil group and 11 in the placebo group). No patients discontinued participation because of lack of efficacy.
  - Patients were severely sleepy at baseline, with mean (SD) sleep latencies on the MSLT of 2.3 (1.6) min for the armodafinil group and 2.4 (1.6) min for the placebo group. The mean KSS score was 7.4 (1.4) in the armodafinil group and 7.3 (1.3) in the placebo group and 97 (87%) of 112 patients in the armodafinil group and 87 (84%) of 104 in the placebo group had a KSS score ≥ 6.
  - Armodafinil significantly improved mean (SD) sleep latency from 2.3 (1.6) min at baseline to 5.3 (5.0) min at final visit, compared with a change from 2.4 (1.6) min to 2.8 (2.9) min in the placebo group ($p < 0.001$).
  - Of 112 armodafinil patients, 89 (79%) were rated as improved on the CGI-C at the final visit compared with 61 (59%) of the 104 placebo patients ($p = 0.001$).
  - The sleep latency for individual MSLT sessions at all 5 time points (midnight to 8:00 AM) at the final visit was greater for patients who received armodafinil than for patients who received placebo ($p < 0.001$ at midnight, 2:00 AM, 4:00 AM; $p = 0.007$ at 6:00 AM; $p = 0.02$ at 8:00 AM).
  - For the armodafinil group, 64 (57%) of 112 patients were very much improved or much improved at the final visit compared with 37 (36%) of 104 patients in the placebo group ($p = 0.002$). The proportion of patients with at least minimal improvement on the CGI-C of sleepiness was significantly greater for armodafinil than for placebo at the 4-week (armodafinil, 89/110 patients [81%]; placebo, 59/100 [59%]; $p < 0.001$), 8-week (armodafinil, 77/99 [78%]; placebo, 45/93 [48%]; $p < 0.001$), and 12-week (armodafinil, 75/96 [78%]; placebo, 50/89 [56%]; $p = 0.001$) assessments.
  - Patient-reported levels of sleepiness during the night shift on the KSS were significantly reduced for the armodafinil group compared with the placebo group at all visits ($p \leq 0.001$ at week 4 and 8; $p \leq 0.01$ at week 12, results shown in graphical form).
  - At the final visit, armodafinil was associated with significant improvement in most items assessed in the electronic diaries, including maximum level of sleepiness during the night shift and commute home and the mean number of mistakes, accidents, or near misses compared with placebo (Table 2).

Table 2. Changes in ratings of sleepiness on the electronic diaries

Characteristic	Placebo (n = 104)			Armodafinil (n = 112)			p-value[c]
	No. of pts[a]	Baseline[b]	Δ from baseline[b]	No. of pts[a]	Baseline[b]	Δ from baseline[b]	
During night shift							

Unintended sleep episodes	88	1.1 (1.0)	-42%	92	1.2 (2.6)	-72%	< 0.001
Intended sleep episodes	79	0.6 (0.6)	-13%	85	0.7 (1.6)	-36%	0.01
Maximum level of sleepiness	99	7.5 (1.0)	-1.1 (1.0)	109	7.5 (1.1)	-2.0 (1.1)	< 0.001
Level of sleepiness during commute home	99	5.9 (1.4)	-0.6 (1.0)	109	5.9 (1.7)	-1.2 (1.2)	0.003
No. of mistakes, near misses, or accidents							
During night shift	66	0.8 (1.0)	-46%	84	1.2 (3.4)	-64%	0.04
During commute home	50	0.3 (0.6)	-47%	60	0.3 (0.4)	-66%	0.12
No. of caffeinated drinks/day	99	1.8 (3.9)	0.0 (1.4)	109	1.3 (1.2)	-0.4 (0.7)	

a Patient numbers represent data from those for whom baseline and post-baseline data were available to calculate change from baseline.
b Values are mean (SD) or percentage.
c Values are based on change from baseline compared with placebo.

- Armodafinil significantly improved standardized memory assessments ($p < 0.001$), mean power of attention ($p = 0.001$), and continuity of attention ($p < 0.001$).
- AEs reported by ≥ 5% of armodafinil patients and more frequently than placebo were headache (15/123 [12%] in the armodafinil group and 12/122 [10%] in the placebo group), nausea (9/123 [7%] in the armodafinil group and 4/122 [3%] in the placebo group), nasopharyngitis (7/123 [6%] in the armodafinil group and 4/122 [3%] in the placebo group), and anxiety (6/123 [5%] in the armodafinil group and 2/122 [2%] in the placebo group). Most AEs were considered mild or moderate.
- Armodafinil did not adversely affect daytime sleep variables (eg, sleep latency, sleep duration, and sleep-stage distribution) compared with placebo.

- **Authors' conclusion:**
  - In patients with excessive sleepiness associated with chronic SWD of moderate or greater severity, armodafinil significantly improved wakefulness during scheduled night work, raising mean nighttime sleep latency above the level considered to indicate severe sleepiness during the daytime. Armodafinil also significantly improved measures of overall clinical condition, long-term memory, and attention.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Cephalon
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Both objective and subjective measures were used to assess efficacy.
  - **Study limitations:**
    - The study was of short duration and did not provide information on long-term efficacy and safety.
    - There is no validated measure for assessing excessive sleepiness in SWD. Although the MSLT is sensitive to changes in sleepiness during nighttime hours and is recommended for assessing sleepiness at night in this population, it has not been specifically validated as a clinical instrument for measuring nighttime sleepiness.
    - The study did not provide assessments of actual work performance or safety.
    - Most patients enrolled were permanent night shift workers. This may limit the generalizability of these results to individuals working alternative shift schedules.
    - This study was performed in SWD patients with both excessive sleepiness and insomnia, who may represent a more severely affected group; therefore, additional studies may be necessary to quantify the effects in a patient population with less severe SWD.
    - The study did not include patients with SWD associated with starting work in the early morning.

Study 7. Czeisler et al. *N Engl J Med*. 2005;353:476-486.

Study Objective: Evaluate the efficacy and safety of modafinil for the treatment of sleepiness in patients with SWD	
Study Design, Follow-up	**Treatment Groups** (N = 209)
• 3-mo, Phase 3, DB, PC, PG, MC, RCT • Patients were evaluated monthly during an overnight laboratory shift after having worked for 3 or more consecutive nights.	• Modafinil 200 mg 30 to 60 minutes before each night shift (n = 99) • Placebo (n = 110)
Inclusion Criteria	**Exclusion Criteria**

• Age 18 to 60 years • Worked each month ≥ 5 night shifts for ≤ 12 hours, with ≥ 6 hours worked between 10:00 PM. and 8:00 AM and ≥ 3 shifts occurring consecutively. • Diagnosis of SWD according to the ICSD • Chronic excessive sleepiness (≥ 3 months) during night shifts • CGI-S rating of moderately ill or worse for sleepiness on work nights, including the commute home from work; an average latency to sleep onset of ≤ 6 during 20-minute nap opportunities at 2-hour intervals during the night, as measured by the MSLT; and a sleep efficiency of ≤ 87.5% as determined by daytime PSG	• Diagnosis by history and/or diagnostic PSG of a concurrent sleep disorder other than chronic SWD • Presence of clinically significant, uncontrolled psychiatric or medical conditions • Abuse of alcohol, narcotics, or other drugs • Caffeine consumption averaging > 600 mg per day within 1 week of baseline • Use of protocol-prohibited prescription medications (eg, any medication that could make a patient feel sleepy, or clinically significant use of over-the-counter [OTC] drugs within 2 weeks of baseline)
Primary Endpoints	**Secondary Endpoints**
• Rating on the CGI-C test for sleepiness during the night shift, including the commute to and from work, at the final visit • Change between baseline and the final visit (ie, at the third month or at withdrawal from the study) in overall mean sleep latency on the basis of results of the nighttime MSLT	• Patient sleepiness assessed using the KSS • Frequency and duration of lapses of attention during performance on the Psychomotor Vigilance Test ○ This endpoint served as a validated and objective measure of alertness at night

- **Results:**
  - Of 209 patients randomized, 204 patients received the drug and153 patients completed the study (placebo, 81; modafinil 72).
  - At baseline, there were no significant differences in demographic variables, shift-work type, sleepiness, performance, and results on PSG between the group that received modafinil and the one that received placebo.
  - Patients were severely sleepy at baseline, with overall mean (±SD) sleep latencies of 2.0 ± 1.8 minutes and 2.1 ± 1.5 minutes for the placebo and modafinil groups, respectively.
  - Seventy-four percent of patients in the modafinil group were rated as at least minimally improved on the CGI-C test at the final visit, as compared with 36% in the placebo group ($p < 0.001$) (Table 3).
  - Overall mean (± standard error of the mean [SEM]) sleep latency, as measured by the MSLT, increased from 2.1 min at baseline to 3.8 min at the final visit with modafinil (change, 1.7 ± 0.4 min; $p < 0.001$) but not with placebo (2.04 at baseline vs 2.37 at the final visit; change, 0.3 ± 0.3; $p = 0.24$). Sleep latency was significantly greater in the modafinil group than in the placebo group ($p = 0.002$). This improvement in sleep latency with modafinil vs placebo was found at 2:00 AM ($p = 0.02$) and 4:00 AM ($p < 0.001$), but not at 6:00 AM ($p = 0.45$) or 8:00 AM ($p = 0.17$).

Table 3. CGI-C at final visit

CGI-C rating	Number (%) of patients	
	Placebo (n = 104)	Modafinil (n = 89)
Very much improved	8 (8)	21 (24)
Much improved	13 (13)	28 (31)
Minimally improved	16 (15)	17 (19)
No change	61 (59)	20 (22)
Minimally worse	4 (4)	2 (2)
Much worse	2 (2)	1 (1)
Very much worse	0 (0)	0 (0)
p-value		< 0.001

  - Differences between modafinil and placebo in the Psychomotor Vigilance Test were statistically significant.
    - The median number of lapses of attention in 20-minute tests during the night was 12.50 at baseline and 10.25 at the final visit for the modafinil group (median change from baseline, -2.6; $p = 0.012$). In the placebo group, the median number of lapses per test bout was 16.13 at baseline and 23.75 at the final visit (median change from baseline, 3.8; $p = 0.008$). The groups did not differ significantly at baseline ($p = 0.797$), but they did differ significantly at the final visit ($p = 0.005$), and the change in lapses of attention during performance of the Psychomotor Vigilance Test from baseline to the final visit was significant for modafinil vs placebo ($p < 0.001$).

- The duration of lapses showed a similar result, decreasing from baseline (780 msec) to the final visit (669 msec) for patients receiving modafinil and increasing from baseline (852 msec) to the final visit (1235 msec) for those receiving placebo; This resulted in a significant difference at the final visit (p = 0.004) and in the change from baseline to the final visit in favor of modafinil vs placebo (p = 0.019).
- Sleepiness levels on the KSS were also significantly reduced for patients receiving modafinil (baseline mean, 7.3; final visit mean, 5.8; change, -1.5 ± 0.2), as compared with placebo (baseline, 7.1; final visit, 6.7; change, -0.4 ± 0.2) (p < 0.001).

○ As compared with placebo, modafinil reduced the maximum level of sleepiness during the night-shift (p < 0.001 for the change from baseline vs placebo) and the level of sleepiness during the commute home (p = 0.01), and 25% fewer patients receiving modafinil reported having had accidents or near accidents during the commute home (p < 0.001). Modafinil treatment during night shifts had no statistically significant effects on unintentional or intentional sleep episodes, mistakes, accidents or near accidents, or caffeine consumption (Table 4).

Table 4. Variables derived from patient diaries

Variable	Placebo (n = 108)			Modafinil (n = 96)			p-value
	Baseline	After baseline	Change	Baseline	After baseline	Change	
During night shift							
Maximum level of sleepiness — score†	7.4±1.0	6.6±1.3	-0.9±1.0	7.3±0.9	5.4±1.5	-1.9±1.4	< 0.001
No. of unintentional sleep episodes†	1.2±1.3	0.6±0.7	-0.6±1.0	1.0±1.1	0.2±0.4	-0.8±0.9	0.20
No. of intentional sleep episodes†	0.5±0.8	0.4±0.5	-0.1±0.5	0.4±0.5	0.2±0.4	-0.2±0.4	0.13
No. of caffeinated drinks consumed†	1.3±1.1	1.1±0.9		1.3±1.2	1.0±1.0		0.10
Patients reporting mistakes, accidents, or near accidents — no. (%)§		59 (55)			46 (48)		0.34
During commute home							
Level of sleepiness — score†	5.9±1.8	5.4±1.7	-0.6±1.2	5.5±1.8	4.4±1.6	-1.1±1.5	0.012
Patients reporting unintentional sleep episodes — no. (%)§		47 (44)			34 (35)		0.24
Patients reporting accidents or near accidents — no. (%)§		58 (54)			28 (29)		< 0.001¶
During days after night shift							
No, of caffeinated drinks consumed‡**	1.0±1.3	0.6±0.7	-0.4±1.0	0.9±1.1	0.7±0.8	-0.2±1.0	0.61
Sleep efficiency — %**††	78.0±20.7	87.5±14.1	9.5±18.3	80.3±19.9	87.5 ±14.4	7.3±18.5	0.55

* Plus–minus values are means ±SD. Patients recorded responses in electronic diaries on actual work nights. Sleepiness scores were obtained with the use of the KSS. Analysis includes patients with baseline values and values after baseline. For each patient, baseline values and values after baseline are average values calculated before and after the start of DB treatment.
† Data were available for 84 patients receiving placebo and for 79 patients receiving modafinil.
‡ p-value is for the change from baseline for modafinil vs placebo.
§ Values are for the number of patients with a value after baseline. Patients were counted once.
¶ p-value is for modafinil vs placebo.
‡ Data were available for 85 patients receiving placebo and for 78 patients receiving modafinil.
** The time interval was from the end of the night shift until 60 minutes after waking up from the last sleep episode.
†† Data were available for 84 patients receiving placebo and for 78 patients receiving modafinil. Sleep efficiency was calculated as the sleep duration divided by the time spent in bed multiplied by 100 so that scores could range from 0 to 100%.

○ During days following night off, there were no significant differences in caffeine use and sleep efficiency between the modafinil and placebo group.
○ There were no significant differences between modafinil and placebo with respect to any measurement of daytime sleep, including sleep duration, latency, and efficiency, and the proportion and distribution of sleep stages.
○ The use of prescription or nonprescription sleeping pills was not specifically monitored, although concomitant use of medications was queried. Of the 96 patients in the modafinil group, 1 reported use of a prescription hypnotic vs none of the 108 placebo patients. Five of the 96 modafinil patients reported use of OTC sleep aids vs 1 of the 108 placebo patients (p = 0.102).
○ Headache was the most common AE reported in both treatment groups.
○ More patients in the modafinil group than in the placebo group had insomnia (6 vs 0%, respectively; p = 0.01).

- **Authors' conclusion:**
  ○ Treatment with 200 mg of modafinil reduced the extreme sleepiness in patients with SWD and resulted in a small but significant improvement in performance as compared with placebo. However, the residual sleepiness that was observed in the treated patients underscores the need for the development of interventions that are even more effective.

- **Study Appraisal:**
  - **Study sponsorship:**
    - Cephalon
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Both objective and subjective measures were used to assess efficacy.
  - **Study limitations:**
    - The study was of short duration and did not provide information on long-term efficacy and safety.
    - There is no validated measure for assessing excessive sleepiness in SWD. Although the MSLT is sensitive to changes in sleepiness during nighttime hours and is recommended for assessing sleepiness at night in this population, it has not been specifically validated as a clinical instrument for measuring nighttime sleepiness.
    - The study did not provide assessments of actual work performance.
    - The vast majority of participants were permanent night shift workers; thus, the study findings are not generalizable to other types of shifts that include nighttime hours.

Pitolisant

Study 8. Dauvilliers et al, *Lancet Neurol.* 2013;12:1068-1075 (HARMONY 1)

Study Objective: Evaluate the safety and efficacy of pitolisant in patients with EDS in narcolepsy	
Study Design, Follow-up	**Treatment Groups** (N = 95)
• Phase 3, AC, DB, double-dummy, PC, PG, MC, RCT • The study was conducted in 32 sleep disorder centers in 5 European countries	• Pitolisant (n = 32) • Modafinil (n = 33) • Placebo (n = 30) • Treatment duration was 8 weeks: 3 weeks of flexible dosing followed by 5 weeks of stable dosing ○ Patients took a low dose of study drug (pitolisant 10 mg or modafinil 100 mg or placebo) during the first 7 days, then a medium dose (pitolisant 20 mg or modafinil 200 mg or placebo) for the next 7 days. ○ On day 14, doses were adjusted on the basis of individual clinical efficacy and safety; no specific recommendations were provided to investigators for dose adjustment. ○ Patients could then receive 10, 20, or 40 mg of pitolisant or 100, 200, or 400 mg of modafinil or placebo. ○ On day 21, investigators could decrease the dose in the case of insufficient tolerance only. ○ Patients continued at their assigned stable dose for an additional 5 weeks. ○ On day 49, patients made a control visit, and treatment was stopped at day 56. Patients then received 1 week of placebo in a withdrawal phase. • Within the pitolisant group, the maximum dose of 40 mg was reached by 61% of patients. • Note: Doses are expressed in terms of the salt form: 5, 10, 20, and 40 mg are equivalent to 4.45, 8.9, 17.8, and 35.6 mg (*Wakix FDA clinical review 2019*).
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy with or without cataplexy and self-reported daily EDS for ≥ 3 months Diagnosis was confirmed by PSG, an MSLT performed within the previous 5 years showing a	• Patients could not have psychostimulants for 14 or more days before baseline but could remain on their anticataplectic drugs (sodium oxybate or antidepressants) at stable doses 1 month before and throughout the trial. • Use of TCAs

mean sleep latency ≤ 8 min with ≥ 2 REM periods, and an ESS score ≥ 14	• Another disorder that could be the main cause of EDS in patients without cataplexy (eg, sleep-related breathing disorder with sleep apnea index ≥ 10 per hr or apnea or hypopnea index of ≥ 15 per hr, or a periodic limb movement (PLM) disorder with arousal index of ≥ 10) • History of substance abuse • Serious CV disorder • Hepatic or renal abnormalities • Psychiatric disorder
Primary Endpoint	**Secondary Endpoints**
• The difference in change in ESS scores between the pitolisant and placebo groups after the 8-week treatment period	• MWT • SART (Appendix G) • CGI-C targeting EDS and cataplexy • EQ-5D (defines health using 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression; overall health is rated on 100-point visual analogue scale [VAS]) (*Herdman et al 2011*) • Patient's global opinion (PGO) of their treatment • Symptoms of cataplexy assessed by patients' sleep diaries（symptoms recorded were sleep attacks, episodes of severe sleepiness, cataplexy attacks, hypnagogic or hypnopompic hallucinations, sleep paralysis, nocturnal awakening, and nocturnal sleep time) • Post-hoc analyses included: ○ Daily cataplexy rate defined as ≥ 1 cataplexy episode during baseline or study treatment period. ○ ESS responder rates defined as patients with a final ESS of ≤ 10

- **Results:**
  - ○ Patients who had at least 1 dose of study drug and provided at least 1 post-baseline value were included in the ITT population.
  - ○ Most of the baseline characteristics were similar among groups. Of the 94 patients included in the ITT analysis, 76 (81%) had a history of cataplexy, 42 (45%) had taken psychostimulants (mostly modafinil or methylphenidate; 13 of 30 patients in the placebo group, 13 of 31 in the pitolisant group, and 11 of 33 in the modafinil group), and 33 (35%) were using anticataplectic drugs and continued them at stable dosage during the trial; of those using anticataplectic drugs, 8 (4 in the placebo group, 2 in the pitolisant group, and 2 in the modafinil group) were on sodium oxybate and 25 used antidepressants. At baseline, the mean daily cataplexy rate was 0.92 in the placebo group, 1.2 in the pitolisant group, and 1.1 in the modafinil group. Fifty-seven (61%) patients were considered still cataplectic during the trial and reported ≥ 1 cataplexy episodes during the trial. The duration of narcolepsy ranged from 10.6 to 14.9 years. The per-protocol (PP) population comprised 79 patients who completed the study: 25 in the placebo group, 26 in the pitolisant group, and 28 in modafinil group.
  - ○ A step-down approach was used for multiple treatment comparisons: superiority of pitolisant over placebo was tested first, then, if shown to be superior, the non-inferiority of pitolisant vs modafinil was tested based on a non-inferiority margin of 2 ESS points.
  - ○ In the ITT analysis, patients in the pitolisant group had a significantly greater improvement from baseline in ESS scores compared with the placebo group (Table 5).
    - ▪ Because the superiority criterion of pitolisant over placebo was met, the non-inferiority of pitolisant to modafinil was tested; the results showed that pitolisant was not non-inferior to modafinil (Table 5).
  - ○ During the trial, ESS decreased at a similar rate in the pitolisant and modafinil groups (data shown graphically). There were no statistically significant between-group differences in analysis of all randomly allocated patients and the PP population (data not shown).
  - ○ MWT values decreased from baseline in the placebo group but improved in the pitolisant group, demonstrating superiority of pitolisant. MWT also improved from baseline in the modafinil group. There was no statistically significant difference between pitolisant and modafinil (Table 5).
  - ○ NO GO error scores in the SART were similar between baseline and end of treatment in the placebo group, whereas they decreased in the pitolisant group, with a statistically significant difference between groups (Table 5).

Changes in the modafinil and pitolisant groups, however, were not statistically different. There were no differences in changes from baseline between either pitolisant and placebo or pitolisant and modafinil in either the SART GO scores or total SART scores (Table 5).

- The proportion of patients who had improvements in EDS assessed by the CGI-C by the end of treatment was largest in the modafinil group and smallest in the placebo group (Table 5). There were little between-group differences in change in severity of cataplexy assessed by the CGI-C.
- EQ-5D values were similar in all 3 groups, whereas PGO on treatment improved only slightly more for pitolisant or modafinil than for placebo (Table 5). The differences were not statistically significant (*Wakix FDA clinical review 2019*).
- The small number of occurrences of other parameters collected in the sleep diaries (hallucinations, sleep attacks, and severe sleepiness) precluded any formal comparison between groups.
- In post-hoc analyses, pitolisant was superior to placebo but not non-inferior to modafinil in terms of improvement in daily cataplexy rate from baseline (Table 5). The percentage reduction in cataplexy rate from baseline to Week 8 was -65% in the pitolisant group, -35% in the modafinil group, and -9% in the placebo group. In other post-hoc analyses, the percentage of responders (with final ESS scores ≤ 10) also differed between the pitolisant and placebo groups and were similar between pitolisant and modafinil (Table 5).

Table 5. Primary and secondary endpoint efficacy results (ITT population)

Endpoint	Placebo		Pitolisant		Modafinil		Treatment difference (MD [95% CI]; p-value)	
	Baseline/final	Δ over trial*	Baseline/final	Δ over trial*	Baseline/final	Δ over trial*	Pitolisant vs placebo (superiority test)	Pitolisant vs modafinil (NI test)
ESS (Δ = final – baseline)	18.9 (2.5)/ 15.6 (4.3)	-3.4 (4.2)	17.8 (2.5/ 12.0 (6.2)	-5.8 (6.2)	18.5 (2.7)/ 11.6 (6.0)	-6.9 (6.2)	-3.0 (-5.6 to -0.4) p = 0.024	0.12 (-2.5 to 2.7); p = 0.250
MWT	8.4 (1.8)/ 7.6 (3.0)	0.88	7.4 (2.3)/ 9.7 (2.8)	1.32	8.8 (2.5)/ 15.1 (2.7)	1.72	1.47 (1.01 to 2.14); p = 0.044	0.77 (0.52 to 1.13); p = 0.173
SART NO GO	8.0 (1.8)/ 8.1 (1.8)	1.0	9.2 (2.0)/ 7.5 (1.9)	0.82	8.5 (2.0)/ 7.1 (1.9)	0.84	0.81 (0.67 to 0.99); p = 0.038	0.97 (0.81 to 1.17); p = 0.765
SART GO	3.5 (0.7)/ 2.7 (0.7)	0.76	3.5 (1.1)/ 2.1 (0.6)	0.6	3.2 (0.7)/ 2.5 (0.6)	0.79	0.79 (0.56 to 1.12); p = 0.176	0.77 (0.54 to 1.20); p = 0.141
SART total	11.5 (2.1)/ 11.4 (2.1)	1.0	12.5 (2.1)/ 10.0 (2.2)	0.8	11.6 (2.1)/ 10.4 (2.2)	0.89	0.80 (0.64 to 1.00); p = 0.053	0.90 (0.71 to 1.14); p = 0.370
CGI-C EDS improved (n/N[%])	--	14/25 (56%)	--	19/26 (73%)	--	24/28 (86%)	--	--
CGI-C cataplexy improved (n/N[%])	--	6/25 (24%)	--	9/26 (35%)	--	8/28 (29%)	--	--
EQ-5D	64 (19.2)/ 70.2 (17.7)	--	65.3 (21.3)/ 73.8 (17.8)	--	58.7 (19.4)/ 72.6 (16.5)	--	--	--
PGO improved (n/N[%])	--	14/25 (56%)	--	24/28 (81%)	--	24/28 (86%)	--	--
ESS responder (post-hoc analysis) (n/N[%])	--	4/30 (13%)	--	14/31 (45%)	--	15/33 (46%)	4.4 (2.1 to 9.2); p < 0.0006	1.0 (0.68 to 1.6); p = 0.908
Cataplexy rate (post-hoc analysis)	0.43 (0.7)/ 0.39 (0.6)	0.92	0.52 (0.6)/ 0.18 (0.4)	0.38	0.4 (0.6)/ 0.26 (0.5)	0.64	0.38 (0.16 to 0.93); p = 0.034	0.54 (0.24 to 1.23); p = 0.138

Abbreviation: NI = non-inferiority
Data are mean (geometric mean) unless otherwise stated
*= change calculated as final-baseline, unless otherwise stated

- The most frequent AEs were headache for the 3 groups, insomnia, abdominal discomfort, and nausea for pitolisant, and abdominal discomfort, nausea, diarrhea, dizziness, anxiety, and irritability for modafinil. There were no clinically relevant between group differences in terms of intensity or resolution of AEs across the 3 groups. Nine AEs reported as severe occurred during the treatment period, of which 6 were deemed treatment-related: 1 with pitolisant (abdominal discomfort) and 5 with modafinil (abdominal pain, abnormal behavior, amphetamine-like withdrawal symptoms, lymphadenopathy, and inner ear disorders).
- No patient receiving placebo or pitolisant experienced a Diagnostic and Statistical Manual of Mental Disorders (DSM)-5-defined withdrawal syndrome during the withdrawal phase compared with 3 patients in the modafinil group.

- **Authors' conclusion:**

- EDS can be improved by pitolisant for at least 2 months, as judged by 2 objective tests in addition to the ESS; pitolisant might also have some anticataplectic activity. Whereas the wake-promoting activity of pitolisant does not differ from that of modafinil, it seems to be better tolerated.

- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet, France (Bioprojet Pharma was acquired by Harmony Biosciences in 2017)
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Pitolisant was tested for superiority to placebo first; if shown to be superior, the non-inferiority of pitolisant vs modafinil was tested. However, the study did not attempt to directly compare the efficacy of pitolisant with modafinil.
    - A treatment difference of -3.0 points on the ESS corresponds to a decrease from severe to moderate EDS and is clinically meaningful (*Wakix FDA summary review 2019*).
    - The secondary endpoint of MWT, although not pre-specified in the statistical analysis plan, provided evidence suggesting that pitolisant had a meaningful effect on an objective measure of sleepiness (*Wakix FDA clinical review 2019*).
  - **Study limitations:**
    - The sample size was small.
    - The study took place only in Europe.
    - The study duration was short and did not provide an assessment of whether tolerance to pitolisant could develop.
    - The flexible dosing scheme and multiple patient visits may have affected the efficacy outcomes with less responsive patients being more likely to be titrated to the highest dose. Parameters for dose titration were not pre-specified, but were left to the investigator's discretion.
    - The data from this single trial did not provide definitive data about dose/dose response. No direct comparisons between the pitolisant 20 and 40 mg doses were conducted (*Wakix FDA clinical review 2019*).
    - Severely ill patients and those with unstable co-morbidities were excluded from the trial; thus, efficacy cannot be extrapolated in these populations.
    - The primary endpoint only included a subjective measure (ESS) of wakefulness.
      - Currently, the ESS scale has fallen out of favor with the FDA because it requires patients to assess a hypothetical situation with which they may or may not have had experience and is subject to recall bias. However, the FDA accepted the ESS for this application based on precedents from other narcolepsy development programs (*Wakix FDA summary review 2019*).
    - Non-inferiority of pitolisant to modafinil was not demonstrated.
    - Cataplexy rate was not assessed as a primary endpoint nor was it a pre-specified secondary endpoint.
    - Patients who were previously receiving modafinil (33% of the trial population) may have been unblinded to treatment assignment due to its effects.
    - Continuation of anticataplectic medications in a subpopulation of patients precludes extrapolation of the study findings to drug-free patients.
    - The study did not detect a difference in QoL scores or overall patient opinion on treatment in pitolisant-treated patients (*Wakix FDA clinical review 2019*).

Study 9. Wakix dossier 2019; Wakix FDA clinical review 2019. NCT 01638403 (HARMONY 1bis) (unpublished)

Study Objective: Evaluate the safety and efficacy of pitolisant in patients with EDS in narcolepsy	
Study Design, Follow-up	**Treatment Groups** (N = 166)
• 8-week, Phase 3, AC, DB, PC, PG, MC, RCT • The study was conducted in 32 sleep disorder centers in 5 European countries (Argentina, Austria, Finland, France, Germany, Hungary, Italy, Spain).	• Pitolisant (n = 67) • Modafinil (n = 66) • Placebo (n = 33) • Doses were flexibly titrated over 3 weeks to a maximum of 20 mg/day pitolisant or 400 mg/day modafinil; at the end of week 3, doses were locked and patients entered a 5-week stable-dose period. ○ For the first 7 days, all patients took a low dose (pitolisant 5 mg, modafinil 100 mg, or placebo), then a medium dose (pitolisant 10 mg, modafinil 200 mg, or placebo) for the next 7 days. On day 14, doses were adjusted based on clinical efficacy and safety.

	• A total of 76% of patients in the pitolisant group reached a dose of 20 mg. • Following the 8-week treatment period, all patients received placebo during the 1-week withdrawal phase.
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy with or without cataplexy according to ICSD-2 (self-reported EDS occurring almost daily) with an ESS score ≥ 14 • Patients had to be free of drugs or discontinue any psychostimulant medications for ≥ 14 days at the start of the baseline period. Patients with severe cataplexy were allowed to remain on their anticataplectic medication at stable dose except TCAs; the authorized anticataplectic treatment had to be administered for ≥ 1 month prior to the trial and doses had to be stable throughout the trial.	• Any disorder that could be the main cause of EDS in patients without cataplexy (eg, sleep-related breathing disorder with apnea index ≥ 10 events/hour, apnea-hypopnea index ≥ 15 events/hour of sleep, PLM arousal index ≥ 10 events/hour, shift work, chronic sleep deprivation, or circadian sleep wake rhythm disorder) • Current or recent (within 1 year) history of a substance abuse or dependence disorder including alcohol abuse • Serious CV disorders • Severe renal or hepatic abnormalities • Psychiatric or neurological disorders • Prior severe AEs to CNS stimulants
Primary Endpoint	**Secondary Endpoints**
• Difference in mean final ESS score between the pitolisant and placebo groups after 8 weeks of treatment	• ESS responder rate (defined as final ESS score ≤ 10 or ESS score reduction ≥ 3) • MWT • SART • CGI-C • EQ-5D • PGO of treatment and symptoms of cataplexy assessed by patients' sleep diaries

- **Results:**
  - Baseline demographics (age [median 40 years], gender [50% male], ethnicity [90% Caucasian]) were similar in the 3 groups, as were symptoms of narcolepsy and baseline severity assessments (mean ESS score ~18). History of cataplexy was present in 50 (75%) patients in the pitolisant group, 50 (77%) in the modafinil group, and 26 (81%) in the placebo group. The duration of narcolepsy ranged from 10 to 15 years. The proportion of patients receiving concomitant medications was similar in the treatment groups (30.8 to 33.3%). No patients were receiving antidepressants. No patients in the pitolisant or modafinil groups were receiving sodium oxybate vs 6% in the placebo group.
  - Twelve patients prematurely withdrew from the study (pitolisant, n = 7; modafinil, n = 3; placebo, n = 2), primarily due to an AE (pitolisant, n = 4; modafinil, n = 1), patient decision (pitolisant, n = 2, modafinil, n = 1, placebo, n = 1), or lack of efficacy (pitolisant, n = 1; placebo, n = 1). There were 163 patients included in the ITT population (pitolisant, n = 66; modafinil, n = 65; placebo, n = 32). One patient in the modafinil group was withdrawn due to not fulfilling the inclusion criteria.
  - For the primary analysis, superiority of pitolisant to placebo was tested first. If pitolisant was superior to placebo (MD of ESS score statistically significant [$p < 0.05$]), then non-inferiority of pitolisant and modafinil was assessed. Non-inferiority was based on lower bound of the 95% CI of the difference (pre-defined non-inferiority value: -2).
  - The pitolisant group had a significantly greater ESS score improvement from baseline compared with placebo, demonstrating superiority. The mean change from baseline in ESS score (±SD) was -4.5 (4.6) for pitolisant and -3.7 (5.6) for placebo (treatment effect: -2.12; 95% CI, -4.10 to -0.14; $p = 0.036$).
  - The mean change from baseline in ESS score (±SD) was -7.8 (5.8) for modafinil.
    - The non-inferiority of pitolisant compared to modafinil could not be concluded (treatment effect: 2.83; 95% CI, 1.10 to 4.55; $p = 0.002$), most likely due to an imbalance between dosages of both drugs and the short treatment period; the upper dose of pitolisant was limited to 17.8 mg daily (one-half the maximum dose allowed in other trials), while modafinil was titrated up to the recommended dosing of 200 mg or 400 mg daily. Between 66% and 79% of patients were taking modafinil 400 mg daily.
  - The ESS responder rate (final ESS score ≤ 10 or ESS score reduction ≥ 3) was significantly greater in the pitolisant group (64.2%) compared to the placebo group (34.4%) (RR 2.10; $p = 0.002$). Pitolisant treatment resulted in fewer ESS responders compared to modafinil (43 [64.2%] vs 50 [76.9%], respectively), but this difference was not statistically significant (RR: 0.86; $p = 0.052$). Superiority of pitolisant was seen over placebo in MWT values. The values decreased from baseline in the placebo group but improved in the pitolisant group ($p = 0.022$). MWT also improved from baseline in the modafinil group; however, no statistically significant difference between pitolisant and

modafinil was seen (p = 0.198). The NO GO error scores in the SART decreased in the pitolisant group, with a statistically significant treatment difference compared with placebo (p = 0.002); changes in the modafinil and pitolisant groups were not statistically different. No significant difference on the EQ-5D scores or PGO was found between pitolisant and the placebo group. Results of the secondary endpoints are shown in Table 6.

Table 6. Secondary endpoint results (ITT population)

Endpoint	Pitolisant (n = 67)	Modafinil (n = 65)	Placebo (n = 32)
ESS responder (final ESS score ≤ 10 or ESS score reduction ≥ 3), n (%)			
Change	43 (64.2%)	50 (76.9%)	11 (34.4%)
Relative risk	Pitolisant vs placebo: 2.10; p = 0.002 Pitolisant vs modafinil: 0.86; p = 0.052		
MWT			
Baseline	6.65	5.84	7.90
Final	7.79	7.45	6.51
Change (ratio of final/baseline)	1.17	1.28	0.82
Treatment effect, ratio of mean change (95% CI)	Pitolisant vs placebo: 1.57 (1.12 to 2.20); p = 0.022 Pitolisant vs modafinil: 1.05 (0.80 to 1.38); p = 0.198		
SART-NO GO			
Baseline	8.21	8.88	7.53
Final	6.73	6.50	7.76
Change (ratio of final/baseline)	0.82	0.73	1.03
Treatment effect, ratio of mean change (95% CI)	Pitolisant vs placebo: 0.77 (0.65 to 0.91); p = 0.002 Pitolisant vs modafinil: 0.92 (0.79 to 1.07); p = 0.259		
SART-GO			
Baseline	3.23	2.94	3.05
Final	2.71	2.33	2.60
Change (ratio of final/baseline)	0.84	0.79	0.85
Treatment effect, ratio of mean change (95% CI)	Pitolisant vs placebo: 0.99 (0.77 to 1.27); p = 0.910 Pitolisant vs modafinil: 0.94 (0.73 to 1.21); p = 0.641		
SART-total			
Baseline	11.08	11.71	10.54
Final	8.90	8.44	9.94
Change (ratio of final/baseline)	0.82	0.74	0.94
Treatment effect, ratio of mean change (95% CI)	Pitolisant vs placebo: 0.83 (0.6 to 0.99); p = 0.043 Pitolisant vs modafinil: 0.93 (0.77 to 1.11); p = 0.407		
Cataplexy rate (arithmetic mean)			
Baseline	0.84	0.87	1.25
Final	1.69	0.79	1.85
Change, MD (± SD)	0.85 (3.75)	−0.33 (1.02)	0.59 (1.16)
Treatment effect, MD (95% CI)	Pitolisant vs placebo: −1.00 (−2.12 to 0.13); p = 0.077 Pitolisant vs modafinil: 0.05 (−0.55 to 0.65); p = 0.865		
CGI-C EDS improved, n (%)	44 (65.7%)	49 (75.4%)	11 (34.4%)
CGI-C cataplexy improved, n (%)	31 (46.3%)	32 (49.2%)	10 (31.3%)
PGO improved, n (%)	14 (20.9%)	28 (43.1%)	9 (28.1%)

- TEAEs were reported in 34 (50.7%) patients in the pitolisant group, 31 (47.7%) patients in the modafinil group, and 13 (39.4%) patients in the placebo group. The most frequent AEs were headache in all 3 groups; nausea, nasopharyngitis, and dizziness in the pitolisant group; nasopharyngitis in the modafinil group; and dizziness, diarrhea, insomnia, and fatigue in the placebo group. There were no serious AEs reported during the study. There were 19 severe AEs, 8 of which were regarded as treatment-related: 5 with pitolisant (cataplexy, n = 2; somnolence, n = 2; abdominal pain, n = 1) and 3 with modafinil (somnolence, migraine, abdominal pain, each n = 1).
- Patients in the placebo group experienced significant decreases from baseline in systolic and diastolic BP compared to those in the pitolisant or modafinil groups. No patients in the pitolisant group were reported to have withdrawal syndrome, whereas 1 patient in the modafinil group and 1 in the placebo group met the criteria for withdrawal syndrome.
- The mean change from baseline in Beck Depression Inventory (BDI) was similar between groups: pitolisant, -1.7; modafinil, -1.3 and placebo, -1.1 (p = 0.547).
  - The BDI Short Form scores indicated presence of depression (≥ 6) or indicated suicide risk (score of > 0 on BDI item G). The BDI-SF is a 13-question self-report measure of depression severity. Scores on each question can

range from 0 to 3 on a Likert scale; the maximum total score on the questionnaire is 39. Scores of 0 to 4 indicate minimal depression, 5 to 7 indicate mild depression, 8 to 15 indicate moderate depression, and 16 to 39 indicate severe depression. The BDI-SF asks about sadness, guilt, energy level, appetite, and depressive cognitions, and Item G asks specifically about suicidal ideation (*Wakix FDA clinical review 2019*).

- **Conclusion:**
  - Pitolisant, dosed up to 20 mg once daily, was efficacious on EDS compared with placebo. The effects of pitolisant (up to a submaximal dose of 20 mg/day) and modafinil (up to 400 mg/day) on all EDS measures did not differ substantially. In addition, all 3 treatments were considered to be well tolerated. Withdrawal syndrome was seen with modafinil but not with pitolisant.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet, France
  - **Study rating:**
    - N/A
  - **Study strengths:**
    - Although not as impressive as the results of the HARMONY I study, a decrease of 2 points on the ESS is still considered clinically meaningful based on published literature. The maximum dose of pitolisant in this study was 20 mg (whereas it was 40 mg in HARMONY I) (*Wakix FDA summary review 2019*).
    - The lack of effect on cataplexy could have been related to the lower maximum dose (20 mg) as compared with the dose in HARMONY 1 and HARMONY CTP (40 mg) (*Wakix FDA clinical review 2019*).
    - The secondary endpoint of MWT, although not pre-specified in the statistical analysis plan, provided evidence suggesting that pitolisant had a meaningful effect on an objective measure of sleepiness (*Wakix FDA clinical review 2019*).
  - **Study limitations:**
    - The sample size was relatively small.
    - The study took place only in Europe.
    - The study duration was short.
    - The trial did not assess persistence of effect after treatment was discontinued (*Wakix FDA clinical review 2019*).
    - The primary endpoint only included a subjective measure (ESS) of wakefulness.
    - Non-inferiority of pitolisant to modafinil was not demonstrated, likely due to the imbalance in pitolisant and modafinil dosing selection.
    - The data from this single trial did not provide definitive data about dose/dose response. No direct comparisons between the pitolisant 20 and 40 mg doses were conducted (*Wakix FDA clinical review 2019*).
    - Cataplexy was not assessed as a primary or a pre-specified secondary endpoint.
    - The study did not detect a difference in QoL scores or overall patient opinion on treatment in pitolisant-treated patients (*Wakix FDA clinical review 2019*).
    - Severely ill patients and those with unstable co-morbidities were excluded from the trial; thus, efficacy cannot be extrapolated in these populations.

Study 10. Dauvilliers et al, *Sleep*. 2019;21;42(11):1-11 (HARMONY 3)

Study Objective: Evaluate the safety and maintenance of efficacy of pitolisant in the long-term in the treatment of EDS in patients with narcolepsy with or without cataplexy	
Study Design, Follow-up	**Treatment Group** (N = 102, 75 with cataplexy)
• 12-month, Phase 3, OL, single-arm, MC, longitudinal, uncontrolled trial • Patients were recruited from 7 centers in France and 1 in Hungary	• Pitolisant • Eligible patients went through a 1-month individual titration period at the initiation of treatment, except for patients coming from the French Compassionate Use Program (CUP) who were already treated by pitolisant and could continue at their established dose at inclusion. • Patients received pitolisant 5 mg once daily for the first 7 days, and 10 mg for the next 7 days. Then, during the third week, the dose could be increased up to 20 mg once daily if safety and tolerability were good and, during the fourth week, doses could be adjusted according to individual benefit/tolerance ratio between 5 to 20 mg once daily. After 1 month, the dose could be increased

	to 40 mg once daily if the investigator judged that the efficacy of 20 mg was not sufficient. Thereafter, the dose remained stable for a 2-month period. During the follow-up visits scheduled in all patients at 3, 6, 9, and 12 months, an individual dose adjustment could be performed again (5, 10, 20, or 40 mg once daily). • Six patients dropped out before being titrated to 40 mg (4 at 1 month and 2 at 3 months).
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy with or without cataplexy and ESS score ≥ 12 ○ When typical cataplexy was not present, an overnight PSG followed by a positive MSLT within the past 5 years had to show a mean sleep latency ≤ 8 minutes with ≥ 2 sleep-onset rapid eye movement periods. • Patients could be naive to pitolisant ("*de novo*" subgroup) or formerly treated with pitolisant ("exposed" subgroup) during previous single-blind or DB studies or have been switched from the CUP to this study.	• Any other cause of daytime sleepiness, including an untreated sleep apnea syndrome sleepiness • History of substance abuse, severe psychiatric, or neurological disorder • Serious CV disorder • Severe hepatic or renal impairment • Use of TCAs or H_1-receptor antagonists
Primary Endpoint	**Secondary Endpoints**
• Incidence of TEAEs at 12 months	• BDI • ESS score and responder rate • CGI-C • EQ-5D • Symptoms in patient sleep diaries (partial and generalized cataplexy attacks, hypnagogic hallucinations, sleep paralysis, and sleep attacks)

• **Results:**

○ The study group included 73 *de novo* patients (52 with cataplexy) and 13 exposed patients (11 with cataplexy) with a period of at least 3 months without pitolisant between a previous participation in a pitolisant trial (except 1 with only a 1-week washout); all 86 patients had an up-titration at the start of the study. The other 16 exposed patients (12 with cataplexy) were directly switched from the French CUP and were included at their previous established dose without titration. Hence the length of exposure to pitolisant was longer for the subgroup of previously exposed patients (mean 548 days ± 308 days) as some of them were treated since more than 1 year in the CUP before being enrolled in this study, whereas "*de novo*" patients were exposed for a maximum of 1 year (mean 260 ± 143 days). Two thirds (N = 68) of treated patients completed the 12-month treatment period: 60.3% of the *de novo* patients (N = 44, 31 with cataplexy) and 82.8% of the previously exposed patients (N = 24, 20 with cataplexy).

○ At inclusion, the subgroup of exposed patients (N = 29), including those already treated in the CUP, had a lower mean ESS score than *de novo* patients. They also had a better health status evaluated with EQ-5D and less depressive symptoms as assessed by a lower BDI score. Eighteen patients of the whole population (17.6%) had history of depression or depressive syndrome, with 9 (8.8%) suffering from an ongoing depression at baseline.

○ During the 12 months of treatment, 52.9% of patients were receiving co-medications, the most frequent being methylphenidate (22.5%) and modafinil (17.6%). The co-medications taken at inclusion remained unchanged during the study in 37% of patients, increased (or new treatment added) in 50%, decreased in 7.4% or were discontinued in 5.5%.

○ At 3 months of treatment, 67.5% (56/83) of patients were taking 40 mg pitolisant QD. At the end of the 12 months, 76.5% (52/68) of the completers were treated with the 40 mg daily dose and among them, 65.4% were on monotherapy.

○ Overall, 34 (33.3%) patients prematurely discontinued the trial, mainly during the first 3 months (31/34), including 29 *de novo* patients (39.7% of this subgroup) and 5 (17.2%) exposed patients.

Safety

○ During the first 12-month treatment period, a total of 58 patients (56.9%) reported 168 TEAEs. The TEAE frequency tended to decrease with time: 54.8% (92/168) were observed during the first 3 months and 12.5% (21/168) during the last 3 months. Overall, 43.5% of TEAEs were considered related to the study drug: migraine (n = 2), insomnia (1), irregular sleep (1), nausea (1), depression (1), rash (1), vertigo (1), libido decrease (1), premature ejaculation

(1), spontaneous abortion (1). The most common TEAEs were headache (11.8%), insomnia (8.8%), weight gain (7.8%), anxiety (6.9%), depression (4.9%), and nausea (4.9%). Most TEAEs were mild to moderate; only 22 (13.1%) were severe, of which only half were considered related to the study drug. Seven patients (6.9%) experienced a serious (all non-life-threatening) TEAE. All serious TEAEs were unrelated to pitolisant, except 1 miscarriage that was possibly related. The proportion of treatment-related TEAEs was twice as great in the subgroup who took additional anti-narcoleptic agents in comparison to patients treated with pitolisant alone (53.7 vs 29.2%; p = 0.012).

- TEAE frequency was not substantially increased or different in subpopulations including the elderly (≥ 65 years of age), patients with depressive symptoms at inclusion, patients with CV or gastrointestinal disorders, renal impairment, hepatic impairment, patients with allergies, patients receiving a concomitant treatment with a possible CYP450 interaction (eg, paroxetine), or patients treated with SSRIs only.
- Five cases of depression were reported during the 12-month treatment period. Two of them were considered related to the study drug. The proportion of patients with moderate or severe depressive symptoms (BDI score ≥ 8) was relatively stable during the trial (16.6% at baseline vs 19.1% at 12 months).

Efficacy

- Sleepiness
  - Compared to baseline, the mean ESS score (± standard error [SE]) decreased from the first month of treatment (-3.37 ± 0.42; n = 93) and continued to decline after 3 (-4.39 ± 0.51) and 6 months (-4.90 ± 0.54). This change occurred at a similar rate in the *de novo* or previously exposed patients. In the whole patient population who completed the 12-month treatment (n = 68), the mean decrease from baseline in ESS score was -4.6 ± 0.59 at the end of the period. With last observation carried forward (LOCF) method applied to the missing data of the whole population (N = 102; ie, taking into account the patients who left the trial before 12 months), the reduction was -4.0 ± 0.49. The decrease was significant whether patients had previously been exposed to pitolisant or not (p < 0.001 for both) and of similar magnitude in both subgroups (-4.2 and -4.9, respectively).
  - At the end of the 12-month treatment period, two-thirds of patients were ESS responders with minimum decrease of 3 units; the highest responder rate was observed in the *de novo* subgroup (70.5%). More than one-third of patients (25/68) had normalized sleepiness (ESS < 11) at 12 months (27.3% for *de novo* patients and 54.2% for exposed patients); their mean ESS score decreased from 15.3 ± 0.6 at baseline to 6.6 ± 0.6 at 12 months. In the 44 patients (among 68) who completed a diary at 12 months, the mean daily number of sleep attacks decreased by 27% (from 1.36 ± 0.21 to 0.99 ± 0.14; change -0.37; 95% CI, -0.80 to 0.06).
- Cataplexy
  - In the subgroup of patients with completed sleep diaries (n = 44), the number of complete (generalized) cataplexy attacks per day decreased by 76% between baseline (0.33 ± 0.25) and 12 months (0.08 ± 0.05): change -0.25; 95% CI, -0.67; 0.17]), and by 65% (from 0.77 ± 0.37 to 0.27 ± 0.08 per day; change -0.49; 95% CI, -1.09 to 0.10) for partial cataplexy. The mean daily number of all (generalized and partial) cataplexy episodes decreased by 68% between baseline and 12 months (1.09 ± 0.53 to 0.35 ± 0.10 per day; p = 0.055). Considering the subgroup of *de novo* patients on pitolisant monotherapy (N = 15), generalized and partial cataplexy attacks were reduced by 80% (0.71 to 0.14 per day) and 82% (0.93 to 0.17 per day), respectively.
- Other symptoms
  - The mean frequency of hallucinations decreased by 54% between baseline and 12 months (from 0.13 ± 0.06 to 0.06 ± 0.03 per day; change -0.06 [95% CI, -0.14 to 0.01]). The mean frequency of sleep paralysis was reduced by 63% (from 0.16 ± 0.06 to 0.06 ± 0.04, change -0.10 [95% CI, -0.21 to 0.00]; p = 0.023). The EQ-5D score improved in *de novo* (from 62.1 ± 2.4 at baseline to 71.2 ± 2.6 at 12 months; p < 0.001) patients and, to a lesser extent, in previously exposed patients (from 71.8 ± 3.0 at baseline to 74.5 ± 2.9 at 12 months). The CGI-C improved for almost all patients who completed the 12-month treatment period (93.2% and 95.6% of *de novo* and exposed patients, respectively). The total duration of nocturnal sleep remained unchanged.

Five-year extension phase (*Wakix dossier 2019*)

- The 5-year extension phase included a total of 77 French patients who received pitolisant; 16 ATU patients had already been treated through the CUP before entering the 5-year extension phase of the study and 61 patients were considered naïve to treatment. The baseline demographics and characteristics were similar between groups.
- The mean length of pitolisant exposure for naïve patients (n = 31) and ATU patients (n = 16) was 799 days and 1859 days, respectively.
- The most commonly reported TEAEs were headache (19.5%), weight gain (18.2%), insomnia (11.7%), anxiety (11.7%), depression (11.7%), and nausea (11.7%).The incidence of TEAEs decreased over time, with the highest incidence during Month 1 (16.6%) and < 10% after Month 6.
- Throughout the entire study extension treatment period, 26 (33.8%) patients reported TEAEs leading to temporary or permanent discontinuation of study treatment. The number of patients with TEAEs was higher in subgroups with pitolisant prescribed as add-on therapy to pre-existing narcolepsy treatments, particularly when added to psychostimulants, and the number of patients with TEAEs was lowest in the pitolisant monotherapy subgroup.

- At enrollment, 15 (19.5%) patients had a history of depression or depressive syndrome. Six new cases of depression occurred during the study, but only 3 were considered to be treatment-related. The overall BDI evaluation did not show any increase in depressive symptom severity.
- EDS, measured by ESS score, decreased during the first 12 months of the study, and the reduction was maintained throughout the 5-year extension. The mean ESS score (±SD) of the overall 5-year extension study population decreased from baseline by -3.47 (4.20) at month 1 and continued to decrease at months 3 and 6, with a mean score reduction (±SD) from baseline of -4.03 (4.70) and -4.22 (4.54), respectively. The reduction in ESS score (±SD) was maintained up to the end of the 12-month period and continued during the extended follow-up period, with −4.41 (5.38) after 2 years of treatment (n = 45), -4.45 (6.16) after 3 years of treatment (n = 38), -4.76 (5.73) after 4 years of treatment (n = 34), and -6.07 (7.19) after 5 years of treatment (n = 14).
- Sleep diaries were collected from all compliant patients who had completed their diaries as requested; this included 34 patients at baseline; 32 patients at month 3; 25 patients at months 12 and 18; 17 patients at year 2; 14 patients at year 3; and 2 patients at year 5. The mean daily number of total and partial cataplexy episodes, as well as hallucinations, improved during the 5-year extension phase; at the end of the first 12-month treatment period, total cataplexy episodes, partial cataplexy episodes, and hallucinations decreased by 87.2%, 60%, and 50%, respectively, and this reduction was maintained throughout the extended follow-up period for patients who continued. Other sleep parameters remained relatively stable or improved slightly.

- **Authors' Conclusion:**
  - Pitolisant was well tolerated and improved most major narcolepsy symptoms when given alone or in combination with other anti-narcoleptic agents for a long period. It remains to be definitively determined whether it constitutes a useful first-line therapy for patients with narcolepsy.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet, France
  - **Study limitations:**
    - There was potential for selection bias, both in the patients who entered the study from the CUP who had been on pitolisant previously, as well as from those who dropped out (nearly one-third), during the 1-year treatment period. Patients already exposed to pitolisant were more likely to be compliant, being *a priori* good responders with good tolerance.
    - Since the study did not include a placebo or a control group, it did not provide conclusive data about the duration of pitolisant's treatment effect (*Wakix FDA clinical review 2019*).

Study 11. Szakacs et al, *Lancet Neurol.* 2017;16:200-207 (HARMONY CTP)

Study Objective: Evaluate the safety and efficacy of pitolisant in patients with narcolepsy with cataplexy	
Study Design, Follow-up	**Treatment Groups** (N = 105)
• 7-week, Phase 3, DB, MC, PC, RCT • The study was conducted in 16 sleep disorder centers in 9 countries (Bulgaria, Czech Republic, Hungary, Macedonia, Poland, Russia, Serbia, Turkey, and Ukraine)	• Pitolisant (n = 54) • Placebo (n = 51) • Treatment included 3 weeks of flexible dosing (5 mg, 10 mg, or 20 mg once daily) followed by 4 weeks of stable dosing (5, 10, 20, or 40 mg once daily). ○ During the flexible dosing period, patients took 5 mg of pitolisant or placebo once a day for the first 7 days, then 10 mg of pitolisant or placebo once a day for the next 7 days. ○ During the week 2 visit, the dose was assessed and could remain at 10 mg, be increased to 20 mg, or decreased to 5 mg by the investigators on the basis of individual clinical efficacy and safety; no specific recommendations were provided to investigators for dose adjustment. ○ At visit 3, investigators adjusted doses again to establish the final dose (5, 10, 20, or 40 mg) for the 4-week stable dosing period. ○ At the end of the stable dosing period, all patients entered a 1-week withdrawal period during which time they received placebo.

	• In the stable dosing phase, 64.8% of patients (35/54) in the pitolisant group received the maximum dose of 40 mg.
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy with cataplexy according to the ICSD-2 criteria • Three or more cataplexies per week and an ESS score ≥ 12 • Ongoing anticataplectic treatment with sodium oxybate or antidepressants was allowed if doses were stable for ≥ 1 month before randomization and throughout the trial.	• Any other disorder with EDS (eg, sleep-related breathing disorder with sleep apnea index ≥ 10 per hr or apnea or hypopnea index of ≥ 15 per hr, or a PLM disorder with arousal index of ≥ 10) • History of substance abuse • Serious CV disorder • History of substance abuse • Serious CV disorder • Severe hepatic or renal abnormalities • Psychiatric disorder • Concomitant use of psychostimulants or sedative medications
Primary Endpoint	**Secondary Endpoints**
• Change in the average number of cataplexy attacks per week between the 2 weeks of baseline and the 4 weeks of stable dosing (WCR).	• WCR changes in patients maintained or not in their anticataplectic treatment • Mean change in ESS score • Proportion of patients with final ESS score ≤ 10 (a validated cutoff) • Proportion of patients with abnormally high cataplexy rate (WCR > 15, a non-validated cutoff corresponding to the median of the sample) • MWT • CGI-C • PGO on efficacy • EQ-5D • Number of days with hallucinations

- **Results:**
  - Baseline demographics and narcolepsy characteristics of the 2 groups were similar. The number of cataplexy episodes per week was 11 in the pitolisant group and 9.2 in the placebo group at pre-screening. The mean ESS score was 17.3 in the pitolisant group and 17.1 in the placebo group. In the previous 3 months, 41% of patients in the pitolisant group had received ≥ 1 anticataplectic medication vs 80% in the placebo group. The percentages of patients continuing anticataplectic medications during the trial were 7% in the pitolisant group and 16% in the placebo group.
  - Five patients from the pitolisant group and 9 patients from the placebo group (13.3%) withdrew from the study; 8 patients did not comply (7 in the placebo group and 1 in the pitolisant group), 4 showed lack of efficacy (2 in each group) and 2 patients from the pitolisant group were unable to continue study visits.
  - The reduction of cataplexy by 75% in the pitolisant group ($WCR_{f/b}$ = 0.25) was significantly higher than in the placebo group (38%; $WCR_{f/b}$ = 0.62; rR = 0.51, 95% CI, 0.44 to 0.60, p < 0.0001, Table 7).
    - In post-hoc analyses, this effect remained significant (all p < 0.0001) for each subgroup of patients receiving 10 mg (n = 7), 20 mg (n = 9), or 40 mg (n = 35) as their stable dose.
    - By comparing WCR in both groups at each week, a significant benefit of pitolisant was observed from week 5, improving until the last week (rR = 0.37, 95% CI, 0.07 to 0.69). In a pre-specified analysis, the effect of pitolisant was unchanged, irrespective of whether patients used concomitant anticataplectic treatment pre-inclusion. The geometric mean of the ratio $WCR_{f/b}$ for patients who were receiving concomitant anticataplectic treatment (rR 0.49, 95% CI, 0.31 to 0.82, n = 12) or did not receive this medication (rR 0.51, 0.11 to 2.28, n = 93) were not significantly different ($p_{interaction}$ = 0.455).
  - Superiority of pitolisant was observed for most of the secondary endpoints (Table 7).

Table 7. Primary and secondary endpoint efficacy results (ITT population)

Endpoint	Pitolisant (n = 54)			Placebo (n = 51)			Treatment effect	
	Baseline	Final	Change	Baseline	Final	Change	Effect (95% CI)	p-value
WCR*	9.15	2.27	0.25	7.31	4.52	0.62	0.51 (0.43 to 0.60)	< 0.0001
WCR > 15 (n/N[%])	15/54 (28%)	4/54 (7%)	--	9/51 (18%)	12/51 (24%)	--	0.05 (0.01 to 0.40)	0.005

ESS score	17.4	12.0	-5.4	17.3	15.4	-1.9	-3.48 (-5.03 to -1.92)	0.0001
ESS responders	--	20/51 (39%)	--	--	9/50 (18%)	--	3.28 (1.08 to 9.92)	0.035
MWT (min)‡	3.54	6.91	1.95	4.08	4.32	1.06	1.85 (1.24 to 2.74)	0.003
Improvement in GCI cataplexy (n/N[%])	--	36/54 (67%)	--	--	17/51 (33%)	--	4.00 (1.54 to 10.38)	0.004
Improvement in CGI EDS	--	37/54 (69%)	--	--	12/51 (24%)	--	7.07 (2.55 to 19.59)	0.0002
Improvement in PGO (score < 3, n/N[%])	--	43/54 (79%)	--	--	22/51 (43%)	--	--	--
EQ-5D sum score†	6.4	6.0	-0.4	6.5	6.4	-0.1	-0.33 (-0.70 to 0.03)	0.075
No. of hallucinations per week*	0.41	0.16	0.39	0.57	0.32	0.57	0.50 (0.31 to 0.83)	0.007

*WRC was the primary outcome; the geometric mean was calculated and 0 values replaced with 0.1; change calculated as the final value/baseline measurement; treatment effect analyzed as a ratio rate derived from Poisson regression after adjusting to baseline.
†Arithmetic mean; change calculated as final measurement-baseline measurement; treatment effect derived from a linear model adjusting for baseline.
‡Geometric means; change calculated as the final value/baseline measurement; treatment effect derived from linear model of log-transformed values and adjusted for baseline. Other statistical analyses used logistical regression to identify odds ratio.

- In the pitolisant group, 19 (35%) patients reported AEs vs 16 (31%) in the placebo group (p = 0.528).
- The most frequent AEs were headache for both treatment groups; irritability, anxiety, and nausea for the pitolisant group; and somnolence for the placebo group.
- Double the number of AEs were considered treatment-related with pitolisant compared with placebo (28% [15 of 54 in the pitolisant group vs 12% [6 of 51] in the placebo group; p = 0.048), but all were of mild-to-moderate intensity, except for 1 case of severe nausea that resolved without sequelae after pitolisant discontinuation.
- BDI score decreased significantly between baseline and end of treatment in the pitolisant group compared with placebo (-1.8 vs -0.8; p = 0.02). Duration of nocturnal awakenings also did not differ significantly between groups. No withdrawal syndrome was reported with pitolisant, although 1 was observed with placebo.

- **Authors' conclusion:**
  - Pitolisant was well tolerated and could be useful to improve not only cataplexy but also EDS and hallucinations in patients with narcolepsy. If confirmed in long-term studies, pitolisant might constitute a useful first-line therapy for cataplexy in patients with narcolepsy, for whom there are currently few therapeutic options.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet, France
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - The study enrolled patients with severe cataplexy.
    - A pre-specified analysis examined the effect of concomitant anticataplectic medication in reducing the WCR.
  - **Study limitations:**
    - The sample size was small.
    - The study duration was short and did not provide an assessment of whether tolerance to pitolisant could develop.
    - The flexible dosing scheme and multiple patient visits may have affected the efficacy outcomes with less responsive patients being more likely to be titrated to the highest dose.
      - A pooled analysis of dose-response conducted by the applicant in the ITT populations in HARMONY 1, HARMONY 1bis, and HARMONY CTP found that pitolisant appeared to have a linear dose-response effect (*Wakix FDA clinical review 2019*).

Study 12. Lehert & Falissard, *Sleep.* 2018;41(12):1-13

Study Objective: Evaluate the safety and efficacy of medical treatments for narcolepsy using a network meta-analysis	
Study Design, Follow-up	**Treatment Groups**
• Network meta-analysis (N = 14 RCTs) • All of the studies were of short duration, from 2 to 12 weeks	• Modafinil (n = 10 RCTs) • Pitolisant (n = 3 RCTs) • Sodium oxybate (n = 4 RCTs) • Ten, 4, and 3 studies compared modafinil, sodium oxybate, and pitolisant with placebo, respectively. Eight

	studies compared only 1 treatment with placebo, whereas the 6 other studies compared multiple treatments, respectively (3 or 4 treatments). For the 4 studies of sodium oxybate, the 2 studied dosages 6 and 9 g/d were compared in 3 studies, whereas the low dose (6 g/d) was only compared with placebo in 1 study. Three studies assessed pitolisant: 2 for the 40 mg and 1 study for the 20 mg dose (unpublished, results available).
Inclusion Criteria	**Exclusion Criteria**
• RCTs enrolling adults with narcolepsy with or without cataplexy • RCTs comparing the identified treatment with placebo, as well as comparisons with other treatments • RCTs that provided data on at least 1 of the following selected outcomes for both efficacy and safety: the ESS, the MWT, number of cataplexy attacks during the treatment exposure, and safety reporting of AEs during the treatment exposure	• Non-randomized trials • Retrospective studies • Trials not assessing ≥ 1 efficacy or safety endpoint
Primary Endpoints	**Secondary Endpoints**
• EDS measured by ESS and MWT • WCR ○ To provide a unique primary endpoint and to reduce type 1 multiplicity in the analysis, the ESS and MWT were combined into the EDS mean Z score, to define the narcolepsy score (NS) as the mean of EDS and WCR Z scores (ESS and WCR used minus their values such that larger values indicated patient improvement).	• Overall safety score (OSS), defined as the TEAE incidence rate during the exposure period • Benefit/risk (B/R) ratio ○ The unitless BR ratio was defined as the residual value of the linear fit between NS and OSS, or the simple ratio NS/OSS.

- **Results:**
  - Network meta-analysis compared the efficacy and safety of multiple treatments, multi-arm studies, and multi-criteria treatment decisions, based on a random-effects model that assumed heterogeneity between studies, with corrections for multi-arm studies.
  - Armodafinil studies were pooled with modafinil studies; however, a comparison between the 2 groups was conducted to confirm the relevance of this method.
  - Treatment ranking by P scores measured the extent of certainty that any one treatment was better than another treatment, averaged over all competing treatments, equivalently with the surface under the cumulative ranking curve (SUCRA) defined as the rank of treatment within the range of treatments.
  - Most of the included trials were acceptable for internal validity, external validity, and statistical methodology.
    - In 1 study, the 2 study arms were selected after 16 weeks of OL modafinil, potentially favoring the modafinil group over the placebo group.
    - In *Black & Houghton 2006* (see study 14), all patients were treated with modafinil at the established dose until randomization, and the abrupt withdrawal from modafinil potentially created an artificially worsened placebo group when treatment arms were changed. In this study, the highest doses of sodium oxybate were given without previous titration, unlike as in other trials, and this may have penalized the drug safety profile.
  - For ESS (12 studies), only 3 interventions reached a significant MD when compared with placebo: pitolisant 40 mg (-3.05; 95% CI, -5.24% to -0.85%; p < 0.001), sodium oxybate 9 g (-2.94; 95% CI, -5.04% to -0.85%; p < 0.001), and modafinil (-2.37; 95% CI, -3.41% to -1.32%; p < 0.001), without statistical differences between them. Homogeneity across studies (p = 0.16), and slight between-design inconsistency (p = 0.02) were found.
  - The MWT (12 studies) measured the mean changes in time (minutes) from baseline. There was significant heterogeneity across studies (p < 0.001), and no between-day design inconsistency (p = 0.601) was found. Significant relative benefits when compared with placebo were found for pitolisant 40 mg (4.88 min; 95% CI, 0.57% to 9.20%; p = 0.009) and modafinil (1.85 min; 95% CI, 0.16% to 3.55%; p < 0.001).
  - Cataplexy was reported in 8 studies, and the difference between treatments was calculated by standardized mean difference (SMD) converted by linear calibration into decrease of weekly rate of cataplexies (DWCR). Significant reductions were observed for pitolisant 40 mg (SMD = -0.52; 95% CI, -0.90% to -0.13%; p < 0.001) (DWCR = -5.9) and sodium oxybate 9 g (SMD = -0.41; 95% CI, -0.79% to 0.032%; p = 0.023) (DWCR = -5.2). No marked or significant heterogeneity across studies (p = 0.51) or between-design inconsistency (p = 0.09) were found.

- **Authors' conclusion:**
  - Modafinil (200 to 400 mg/d), sodium oxybate 9 g/d, and pitolisant up to 40 mg/d had similar efficacy in reducing EDS. Only sodium oxybate 9 g/d and pitolisant up to 40 mg/d demonstrated a comparable beneficial effect on cataplexy. Overall, pitolisant at a maximal dose of 40 mg/d was shown to have a slightly better safety profile and the highest BR ratio.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet Pharma
    - The authors are consultants for Bioprojet Pharma.
  - **Study rating:**
    - N/A
  - **Study strengths:**
    - The network meta-analysis compared 6 different interventions involving placebo, modafinil, pitolisant, and sodium oxybate.
  - **Study limitations:**
    - Sodium oxybate and pitolisant were both compared with placebo and modafinil, but not between each other. Methodological issues exist for comparing sodium oxybate in the context of RCTs; unlike the other drug treatments, sodium oxybate induces deep sleep and has multiple contraindications, which would make blinding difficult or impossible.

Sodium oxybate/oxybate salts

Narcolepsy with cataplexy

Study 13. Alshaikh et al, *J Clin Sleep Med.* 2012;8(4):451-458

Study Objective: Evaluate the efficacy and safety of sodium oxybate in narcolepsy-cataplexy patients	
Study Design, Follow-up	**Treatment Groups** (N = 741)
• Systematic review and meta-analysis (N = 6 RCTs and 5 companion reports) • The duration of the RCTs ranged from 4 to 8 weeks, except for 1 study that lasted for 12 weeks. Sodium oxybate at a dose range between 4.5 to 9 g/night was the dose evaluated in most of the studies.	• Sodium oxybate • Placebo • Modafinil • One study assessed the combination of sodium oxybate and modafinil vs sodium oxybate and modafinil alone.
Inclusion Criteria	**Exclusion Criteria**
• RCTs evaluating sodium oxybate in patients with narcolepsy and cataplexy (published or unpublished)	• Non-RCTs
Primary Endpoint	**Secondary Endpoints**
• Elimination of EDS according to subjective or objective indicators.	• QoL using the SF-36 scale • CGI-C

- **Results:**
  - All of the included studies excluded patients with other sleep disorders. The percentage of females ranged from 50 to 65%. One study that assessed the effect of sodium oxybate on EDS did not include cataplexy as an enrollment criterion.
  - None of the included RCTs were assessed as having adequate sequence generation or allocation concealment. All of the studies adequately blinded participants and addressed incomplete outcome data. Five of the 6 studies were free from selective outcome reporting. All of the studies scored unclear on other biases, as they involved private-industry funding. Four of the included studies were sponsored by the manufacturer.
  - Sodium oxybate (usually 9 g/night) was superior to placebo for reducing mean weekly cataplexy attacks (n = 2 RCTs, MD -8.46, 95% CI, -15.27 to -1.64), heterogeneity: I^2 = 0%, test for overall effect: Z = 2.43 [p = 0.01]); increasing the MWT (n = 2 RCTs, MD 5.18, 95% CI, 2.59 to 7.78, I^2 = 0%, Z = 3.93 [p < 0.0001]); and reducing sleep attacks (n = 2 RCTs, MD -9.65, 95% CI, -17.72 to -1.59), I^2 = 13%, Z = 2.35 [p = 0.02]).
  - Data from 3 RCTs indicated an increase in CGI-C scores (RR 2.42, 95% CI, 1.77 to 3.32, I^2 = 0%, Z = 5.53 [p < 0.00001).
  - Sodium oxybate did not significantly increase REM sleep vs placebo (n = 2 RCTs, MD -0.49, 95% CI, -3.90 to 2.92, I^2 = 0%, Z = 0.28 [p = 0.78]).

- Patients receiving sodium oxybate (9 g per night) experienced more AEs vs placebo, including nausea (n = 3 RCTs, RR 7.74, 95% CI, 3.15 to 19.05, I^2 = 0%, Z = 4.45 [p < 0.00001]), vomiting (n = 2 RCTs, RR 2.87, 95% CI, 0.84 to 9.80, I^2 = 10%, Z = 1.69 [p = 0.09]), dizziness (n = 3 RCTs, RR 11.83, 95% CI, 1.56 to 89.43, I^2 = 0%, Z = 2.39 [p = 0.02]) and enuresis (n = 2 RCTs, RR 4.32, 95% CI, 1.14 to 16.41, I^2 = 52%, Z = 2.15 [p = 0.03]).

- **Authors' conclusion:**
  - Patients with narcolepsy on sodium oxybate showed a significant reduction in cataplexy based on diaries and significant improvement in EDS based on objective (MWT) and validated subjective (ESS) assessment methods. Sodium oxybate was well tolerated in patients with narcolepsy, and most AEs were mild to moderate in severity.
- **Study Appraisal:**
  - **Study sponsorship:**
    - This was not an industry supported study. The authors declared no financial conflicts of interest.
  - **Study rating:**
    - N/A
  - **Study strengths:**
    - All meta-analyses had minimal statistical heterogeneity (p > 0.1).
  - **Study limitations:**
    - The included trials had small sample sizes.
    - Due to the short study durations, long-term efficacy and safety could not be assessed.
    - Publication bias could not be assessed because there were too few trials in the meta-analysis.
    - In the pivotal trials of sodium oxybate, the majority of patients (80 to 85%) were receiving concomitant CNS stimulants. The high percentages of concomitant stimulant use make it impossible to assess the efficacy and safety of sodium oxybate independent of stimulant use (*Xyrem prescribing information 2018*).

Narcolepsy

Study 14. Black & Houghton, *Sleep.* 2006; 29(7):939-946

Study Objective: Evaluate the efficacy of sodium oxybate, modafinil, and the combination of the two for EDS in narcolepsy patients previously taking modafinil	
Study Design, Follow-up	**Treatment Groups** (N = 222 [ITT population])
• DB, PC, PG, MC, RCT • Visit 1: patients were evaluated for trial inclusion (1 to 2 weeks) • Visit 2: occurred 1 to 2 weeks later when overnight PSG was performed followed by the MWT; patients remained on established doses of modafinil and any other concomitant medications (14 ± 4 days) • Visit 3: included baseline PSG and MWT recordings before beginning the treatment phase according to prior DB randomization (28 ± 4 days) • Visit 4: efficacy and safety assessments were performed including PSG and MWT measurements (28 ± 4 days) • Visit 5: final efficacy and safety assessments were performed	• Placebo (n = 55) (Group 1) • Sodium oxybate (n = 50) (Group 2) • Modafinil (n = 63) (Group 3) • Modafinil + sodium oxybate (n = 54) (Group 4) • Patients randomly assigned to Groups 3 and 4 continued to receive their customary doses of modafinil in blinded fashion. Patients randomly assigned to Groups 2 and 4 received sodium oxybate at a dose of 6 g nightly, administered in 2 equally divided doses at bedtime and again 2.5 to 4 hours later for the initial 4-week period of the study. Patients in Groups 1 and 3 received an equivalent volume of placebo sodium-oxybate solution. • Patients returned to the clinic for Visit 4, 4 weeks after efficacy and safety assessments were performed. Patients continued taking modafinil or placebo modafinil at their prescribed dose; however, the dose of sodium oxybate was increased to 9 g nightly in 2 equally divided doses. Patients assigned to placebo sodium oxybate increased their dose of placebo solution by an equivalent volume. All patients continued taking their assigned drug regimen for an additional 4 weeks before returning to the clinic for final efficacy and safety assessments at Visit 5.
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy according to the ICSD criteria • Taking a stimulant medication for the treatment of EDS for ≥ 3 months and taking stable doses of modafinil 200 to 600 mg/day for ≥ 1 month immediately prior to	• Use of sodium oxybate or any investigational therapy within the 30-day period prior to enrollment • Sleep apnea disorder • Any other cause of EDS such as periodic limb movements of sleep (PMLS)

the trial or were taking stable doses of modafinil for ≥ 6 weeks prior to trial entry	• Concurrent use of hypnotics, tranquilizers, sedating antihistamines, benzodiazepines, anticonvulsants, or clonidine • Current or recent history of a substance abuse disorder • Serum creatinine > 2.0 g/dL • Alanine aminotransferase or aspartate aminotransferase > twice the upper limit of normal (ULN) • Bilirubin > 1.5 times the ULN • History of clinically significant dysrhythmia or history of myocardial infarction within the prior 6 months • History of seizure disorder, clinically significant head trauma, or past invasive intracranial surgery • Occupation requiring variable shift work or routine night shifts
Primary Endpoint	**Secondary Endpoints**
• MWT	• ESS • CGI-S • CGI-C

- **Results:**
  - A total of 278 patients were enrolled in the study, of which 231 were randomly assigned to 1 of the 4 treatment groups. The ITT population consisted of 222 patients who received at least 1 dose of DB medication.
  - Compared with the placebo group, the other 3 treatment groups maintained significantly longer mean average daytime sleep latencies after 8 weeks of treatment, as determined by the MWT (Table 8). From the beginning of the baseline period to the end of the DB treatment period, the placebo group demonstrated a significant within-group decrease in sleep latency of 2.72 min as a consequence of withdrawal from modafinil. In contrast, neither the sodium oxybate nor the modafinil groups demonstrated within-group changes in sleep latency at the end of the trial (ie, there were no significant differences between the 2 groups). The mean average sleep latency for both groups was significantly longer than that of placebo-treated patients at the end of the trial. The sodium oxybate/modafinil group demonstrated a mean average sleep latency increase of 2.68 min, compared with baseline, representing the incremental improvement in EDS produced by the addition of sodium oxybate over the response produced by modafinil alone.
  - The sodium oxybate and sodium oxybate/modafinil groups demonstrated significant reductions in ESS scores, compared with placebo at the end of the trial (for each, $p < 0.001$) whereas the scores for the modafinil-treated patients did not significantly change and were not different from the placebo group (Table 9). In the sodium-oxybate group, following the discontinuation of modafinil, the ESS scores decreased from a median average of 15 to 12 by the end of the 8-week DB treatment phase and, similarly, from 15 to 11 in the sodium oxybate/modafinil group (for each, $p < 0.001$ compared with baseline). In contrast, the placebo group demonstrated no change in ESS scores during the same period.

Table 8. Results for MWT[a]

MWT	Placebo (n = 55)	Sodium oxybate (n = 50)	Modafinil (n = 63)	Sodium oxybate + modafinil (n = 54)
Visit 3	9.74 ± 6.57 (n = 55)	11.29 ± 6.40 (n = 49)	10.48 ± 6.03 (n = 63)	10.43 ± 6.77 (n = 54)
Visit 5	6.87 ± 6.14 (n = 53)	11.97 ± 7.21 (n = 48)	9.86 ± 5.89 (n = 62)	13.15 ± 6.91 (n = 53)
Change[b]	-2.72 ± 4.54	0.58 ± 5.68	-0.53 ± 4.36	2.68 ± 5.07
p-value[c]	--	< 0.001	0.006	< 0.001

[a]Data are presented as the mean average of 4 trials per patient ± SD, in minutes, LOCF. Visit 3 followed 2 weeks of SB modafinil at previously established doses. Visit 5 followed 4 weeks of placebo or sodium oxybate 9 g nightly and/or modafinil at previously established doses.
[b]Change from Visit 3 to Visit 5
[c]Compared with placebo

Table 9. Results for ESS[a]

ESS	Placebo (n = 55)	Sodium oxybate (n = 50)	Modafinil (n = 63)	Sodium oxybate + modafinil (n = 54)
Visit 3	16.0 (n = 54)	15.0 (n = 48)	14.0 (n = 61)	15.0 (n = 54)

Visit 4	17.0 (n = 53)	13.0 (n = 48)	15.0 (n = 62)	11.5 (n = 50)
p-value	--	< 0.001	0.071	< 0.001
Visit 5	16.0 (n = 53)	12.0 (n = 49)	15.0 (n = 63)	11.0 (n = 53)
p-value	--	< 0.001	0.767	< 0.001

[a]Data are presented as median average, in minutes, LOCF. Visit 3 followed 2 weeks of SB modafinil at previously established doses. Visit 4 followed 4 weeks of placebo or sodium oxybate 6 g nightly and/or modafinil at previously established doses. Visit 5 followed 4 weeks of placebo or sodium oxybate 9 g nightly and/or modafinil at previously established doses. Significance was as compared with placebo.

- The patients in the sodium oxybate and sodium oxybate/modafinil groups had significantly fewer weekly sleep attacks at the end of the trial, as compared with modafinil and placebo groups. In the sodium oxybate group, sleep attacks decreased from a mean of 10.05 at baseline to 7.10 after 8 weeks ($p < 0.001$) and the sodium oxybate-modafinil group demonstrated a decrease from 11.82 to 5.55 ($p < 0.001$). There was no significant difference between the modafinil- and placebo-treated groups.
- The baseline CGI-S assessment indicated that the patients enrolled in the study were considered to be markedly ill despite treatment with modafinil. At the end of the trial, the sodium oxybate group and sodium oxybate-modafinil group each demonstrated overall improvements in their clinical condition, compared with the placebo group ($p = 0.002$ and $p = 0.023$, respectively). In contrast, the placebo and modafinil groups were judged as demonstrating no significant change in disease severity.
- Based on the CGI-C, a significantly higher percentage of patients in the sodium oxybate and sodium oxybate-modafinil groups had a successful treatment response. Compared with the placebo group, 48.0% ($p = 0.002$) of the sodium oxybate group and 46.3% ($p = 0.023$) of the sodium oxybate-modafinil group were judged to be much improved or very much improved, compared with 21.8% of the placebo group and 19% of the modafinil group.
- Compared with the incidence of AEs reported in the sodium oxybate (60%), modafinil (54.0%), or placebo groups (69.6%), a somewhat greater number of AEs were reported in the sodium oxybate-modafinil group (78.9%). Among all patients, the most common TEAEs included headache (15.2%), nausea (11.7%), dizziness (9.1%), nasopharyngitis (6.1%), vomiting (6.1%), and somnolence (5.6%).
- Nausea and vomiting occurred with the highest frequency in the sodium oxybate groups (1.8% for placebo; 21.1% for sodium oxybate; 3.2% for modafinil; 21.1% for sodium oxybate-modafinil), whereas the incidence of dizziness was highest in the sodium oxybate-modafinil group (21.1% vs 5.4% for placebo, 7.3% for sodium oxybate, and 3.2% for modafinil). Statistically significant differences between treatment groups were also noted with respect to tremor (0% for placebo, 5.5% for sodium oxybate, 0% for modafinil, 14.0% for sodium-oxybate-modafinil) and paresthesia (0% for placebo, 7.3% for sodium oxybate, 0% for modafinil, 3.5% for sodium oxybate-placebo), and upper respiratory tract infections, occurring primarily in the placebo group.
- The number of patients who withdrew from the study early was highest in the sodium oxybate-modafinil group (n = 6) compared with sodium oxybate (n = 4), modafinil (n = 2), or placebo groups (n = 1).

- **Authors' conclusion:**
  - Sodium oxybate and modafinil are both effective for treating EDS in narcolepsy, producing additive effects when used together. Sodium oxybate is beneficial as both monotherapy and as adjunctive therapy for the treatment of EDS in narcolepsy.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Orphan Medical Inc.
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - The study used both objective and patient-reported validated outcome measures.
  - **Study limitations:**
    - The trial duration was short.
    - The study population was already being treated with modafinil for 3 months or longer prior to trial entry. Thus, AEs due to modafinil may have been underrepresented in these patients because only patients who were able to tolerate the medication entered the trial.
    - It is unknown whether the patients were partial responders or non-responders to modafinil prior to trial entry.

Study 15. U.S. Xyrem Multicenter Study Group. *Sleep Med*. 2004;5(2):119-123.

- Fifty-five narcoleptic patients with cataplexy who had received continuous treatment with sodium oxybate for a minimum of 6 months (range, 7 to 44 months, mean 21 months) in a long-term, OL sodium oxybate safety trial were enrolled in a DB treatment withdrawal study. Patients were previously stabilized on sodium oxybate using individualized doses providing optimum clinical effect, ranging from 3 to 9 g nightly. A 2-week SB sodium oxybate treatment phase established a baseline for the weekly occurrence of cataplexy. This was followed by a 2-week DB

phase in which patients were randomized to receive unchanged drug therapy (n = 26) or placebo (n = 29). The primary endpoint was the change in the number of weekly cataplexy attacks from the baseline to the DB treatment phase.

- In the sodium oxybate group, there was no median change in the number of cataplexy attacks between the 2-week SB baseline phase and the 2-week DB phase. In contrast, cataplexy attacks increased by a median of 21.0 in the placebo patients during the same 2-week period ($p < 0.001$); median change from baseline was 39.0 for the placebo group and 16.5 for the sodium oxybate group. The mean (SD; range) frequency of weekly cataplexy attacks over the 2-week baseline period increased from 15.8 (39.9; 0 to 197) to 46.4 (73.8; 0 to 250) at the end of the 2-week DB phase for patients receiving placebo; in patients receiving sodium oxybate, the number of cataplexy episodes was 9.9 (21.4; 0 to 93) and 12.8 (33.5; 0 to 158) at the same time points. There was no evidence of rebound cataplexy in patients who were randomized to placebo following long-term use of sodium oxybate.
- During the SB phase of the study, AEs were reported in 17 (31%) patients. During the DB phase, AEs were reported by 12 (22%) patients, including 3 patients in the sodium oxybate group, and 9 in the placebo group. No AE led to discontinuation and none were serious.
- The authors concluded that this controlled trial provides evidence supporting the long-term efficacy of sodium oxybate for the treatment of cataplexy. In contrast with antidepressant drug therapy, there is no evidence of rebound cataplexy upon abrupt discontinuation of treatment.

Pediatric Study

Study 16. Plazzi et al, *Lancet Child Adolesc Health*. 2018;2(7):483-49

Study Objective: Evaluate the safety and efficacy of sodium oxybate oral solution treatment in children and adolescents with narcolepsy with cataplexy

Study Design, Follow-up	**Treatment Groups** (N = 106)
• DB, PC, RW, MC, OL study • The study took place in 30 sites in 5 countries (U.S., Finland, France, Italy, and the Netherlands) • Randomization was balanced for age group (7 to 11 years and 12 to 17 years), previous sodium oxybate treatment (taking sodium oxybate at study entry and sodium oxybate -naive), and location (U.S. and European Union).	• Sodium oxybate in 2 divided doses (bedtime and 2.5 to 4 hours later) (n = 31) • Placebo (n = 32) • Sodium oxybate-naïve patients underwent a dose titration period of 3 to 10 weeks in which they were titrated to an effective and tolerable (optimal) dose that achieved a state of cataplexy stability. • Once an optimal dose was achieved, patients entered a stable dose period of 2 weeks. • After the screening period, patients who were taking sodium oxybate at study entry did not undergo titration and entered the stable-dose period. • During the stable dose period, sodium oxybate-naive patients remained on their established optimal dose for 2 weeks. • Patients taking sodium oxybate at entry remained on their previously established dose for 3 weeks. Efficacy assessments were based on the last 2 weeks of the stable dose period. Patients treated with stimulants or wake-promoting agents remained on the same dose during the stable-dose and DB treatment periods. • During the DB treatment period, participants randomly assigned to sodium oxybate remained on the dose and regimen used in the stable-dose period and patients randomly assigned to placebo were administered placebo at a volume and regimen equivalent to the dose and regimen of sodium oxybate taken during the stable-dose period.
Inclusion Criteria	**Exclusion Criteria**
• Patients 7 to 16 years of age at screening with primary diagnosis of narcolepsy with cataplexy as defined by either the ICSD-2 or ICSD-3 criteria, either being treated with sodium oxybate or sodium oxybate-naïve at study entry	• Previous use and discontinuation of sodium oxybate because of no efficacy or poor tolerability • Narcolepsy secondary to another medical condition • History of seizure disorder or head trauma associated with loss of consciousness

• History of ≥ 14 cataplexy attacks in a typical 2-week period, and clinically significant EDS before any narcolepsy treatment was required • If currently treated with sodium oxybate, receiving unchanged doses (twice nightly dosing ≤ 9 g/night) of sodium oxybate for at ≥ 2 months prior to screening with reported clinical improvement of cataplexy	• Clinically significant parasomnia disorder • Evidence of sleep-disordered breathing or hypoventilation • Past or current major thought disorder • Current clinically significant depression or suicidal risk • Concomitant use of sedative hypnotic or anxiolytic medications • Medications with anticataplectic effects (eg, SSRIs, or TCAs) were discontinued ≥ 1 month before study screening. Participants entering the study taking stimulant or wake-promoting medications were allowed to continue these medications.
Primary Endpoint	**Secondary Endpoints**
• Change in weekly number of cataplexy attacks from the last 2 weeks of the stable-dose period (baseline) to the 2 weeks of the DB treatment period	• Change in the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) score from the end of the stable dose period to the end of the DB treatment period • CGI-C for cataplexy severity • CGI-C for narcolepsy overall • Change in QoL using SF-10 Health Survey for Children

- **Results:**
  - Two sodium oxybate-naive patients did not take the study drug and discontinued from the titration period. Sixty-seven (91%) of the sodium oxybate-naive patients were titrated to an optimal dose and entered the stable-dose period. Sixty-three patients (the efficacy population) entered the DB treatment period before the protocol amendment that discontinued the placebo group.
  - Baseline demographics were similar between the sodium oxybate and placebo groups. The median age was 12 years (range, 7 to 17); 73 (69%) of the 106 enrolled patients were White and 63 (59%) were male. At study entry, 74 (70%) patients were sodium oxybate-naive, and 32 (30%) patients were treated with sodium oxybate for a median of 12 months (range, 2.0 to 52.0).
  - At study entry, the median ESS-CHAD score was 14 (moderate daytime sleepiness; range, 5 to 22), and 43 (41%) participants had ESS-CHAD scores ≥ 16. Previous stimulant or wake-promoting medications were used by 53 (50%) patients at study entry. Stimulant or wake-promoting medications were taken by 55 (56%) patients during the stable-dose period, and by 53 (56%) patients during the DB treatment period (56% of patients in the placebo group and 55% of patients in the sodium oxybate group). The median dose of sodium oxybate taken during the stable-dose period was 7.0 g per night (range, 3.0 to 9.0 g per night).
  - Results of the preplanned interim analysis of the primary endpoint (n =35) showed that efficacy was achieved ($p = 0.0002$). Results of the full efficacy analysis (n = 63) showed that patients who were withdrawn from sodium oxybate treatment and randomly assigned to placebo during the DB treatment period had a significant increase in the number of weekly cataplexy attacks compared with patients who were randomly assigned to continue treatment with sodium oxybate. The median change from baseline in the weekly number of cataplexy attacks was 12.7 (Q1, Q3 = 3.4, 19.8) for patients randomly assigned to placebo and 0.3 (-1.0, 2.5) for patients randomly assigned to continue treatment with sodium oxybate ($p < 0.0001$). Additionally, patients receiving placebo had an increased number of cataplexy attacks at week 1, which further increased at week 2.
  - Results of the CGI-C showed that patients who received placebo were rated as having worse cataplexy severity than were patients continuing sodium oxybate treatment. The mean change in CGI-C score for cataplexy severity for the placebo group was -1.5 (SD 1.2) vs -0.4 (1.1) for the sodium oxybate group ($p = 0.0006$).
  - The median change from baseline in ESS-CHAD scores was greater in the placebo group (3.0 [Q1, Q3 = 1.0, 5.0]), indicating increased sleepiness, compared with the sodium oxybate group (0.0 [-1.0, 2.0]; $p = 0.0004$).
  - Results of the CGI-C for narcolepsy overall showed a worsening of narcolepsy in patients randomly assigned to placebo ($p = 0.0008$), with 59% as much worse or very much worse, compared with 10% in patients continuing sodium oxybate treatment ($p < 0.0001$).
  - No significant difference was observed on the SF-10.
  - Generally, results of subgroup analyses by age group and by sodium oxybate status at study entry were similar to the primary analyses for weekly cataplexy attacks and CGI-C for cataplexy severity. These results showed an increased change from baseline (last 2 weeks of the stable-dose period) to the DB period in weekly cataplexy attacks and worsening CGI-C scores for cataplexy severity for patients randomly assigned to placebo; however, ESS-CHAD scores were not significantly different between treatments in the younger age group or in patients taking sodium oxybate at study entry.

- Commonly reported (> 5%) AEs were enuresis (15/72 [21%] sodium oxybate-naive patients vs 4/32 [13%] taking sodium oxybate at study entry), nausea (16 [22%] vs 2 [6%]), vomiting (15 [21%] vs 2 [6%]), headache (13 [18%] vs 4 [13%]), decreased weight (11 [15%] vs 1 [3%]), decreased appetite (8 [11%] vs none), nasopharyngitis (7 [10%] vs none), and dizziness (5 [7%] vs 1 [3%]). Two serious AEs (1 event of severe acute psychosis and 1 event of moderate suicidal ideation) were reported, and both were considered to be related to the study drug. There were no reported deaths.

- **Authors' Conclusion:**
  - The study results supported the clinical efficacy of sodium oxybate for the treatment of both EDS and cataplexy in narcolepsy in children. The safety profile of sodium oxybate was consistent with that observed in adult patients.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Concomitant stimulant or wake-promoting agents were allowed, which could be considered more representative of real-world clinical practice, in which they are commonly prescribed in addition to sodium oxybate.
  - **Study limitations:**
    - Potential participants who had tried and failed on sodium oxybate previously were excluded.
    - Patients with mild cataplexy (< 14 attacks per typical 2-week period) were excluded.
    - There were fewer patients in the younger age group (7 to 11 years) than in the older age group.
    - Efficacy during the DB, RW period might have been underestimated because of the short duration (2 weeks). Findings from subgroup analyses of ESS-CHAD in patients aged 7 to 11 years and taking sodium oxybate at entry were not significant, and there were fewer patients in these groups.
    - Subgroup analyses were limited by the small number of patients completing the DB period.
    - The study was limited to patients with narcolepsy with cataplexy.

Study 17. Xywav dossier 2020 (unpublished)

Study Objective: Evaluate the safety and efficacy of oxybate salts in adults with narcolepsy with cataplexy	
Study Design, Follow-up	**Treatment Groups**
• DB, PC, RW, MC study • The study was conducted in the U.S. and Europe. • The main study consisted of a ≤ 30-day screening period (N = 255); a 12-week, OL, optimized treatment and titration period to transition to oxybate salts from previous medications for the treatment of cataplexy (N = 201); a 2-week stable-dose period (N = 149); a 2-week DB, RW period (N = 136); and a 2-week safety follow-up. • During the screening period, patients were categorized in the following groups based on their medication use for the treatment of cataplexy at study entry: ○ Sodium oxybate only group ○ Sodium oxybate + other anticataplectics group ○ Other anticataplectics group ○ Cataplexy treatment-naïve group	• DB, RW period: ○ Oxybate salts (n = 69) ○ Placebo (n = 67) • Enrolled patients entered the 12-week, OL optimization and titration period and initiated oxybate salts treatment, with dose titration as needed to optimize efficacy and tolerability. ○ Patients treated with sodium oxybate monotherapy or in combination with other anticataplectics at screening were initiated on a g-to-g equivalent dose of oxybate salts and remained on that same dose for the first 2 weeks. ○ Patients naïve to sodium oxybate initiated oxybate salts at 4.5 g/night and titrated to an optimal dose, with a maximal increase of up to 1.5 g/night/week. ○ Patients taking other anticataplectics at study entry, with or without sodium oxybate, continued taking their other anticataplectics for the first 2 weeks, followed by a taper of other anticataplectics until discontinuation by week 10. • The OL optimized treatment and titration period was followed by a 2-week stable-dose period, during which efficacy assessments were performed while each patient received a stable dose of oxybate salts. At the end of the stable-dose period, patients were randomized 1:1 to receive placebo or to continue oxybate salts treatment.

	Randomization was stratified by treatment for cataplexy at study entry.
Inclusion Criteria	**Exclusion Criteria**
• Patients 18 to 70 years of age with a primary diagnosis of narcolepsy with cataplexy meeting ICSD-3 criteria or DSM-5 criteria and currently untreated or treated with or without anticataplectics • History of ≥ 14 cataplexy attacks in a typical 2-week period prior to receiving any narcolepsy treatment • If patients were receiving medication(s) for the treatment of cataplexy at study entry, the medication regimen was to be stable for ≥ 2 months prior to study entry; if patients were taking wake-promoting agents or stimulants at study entry, they had to be taking stable doses for ≥ 2 months prior to study entry and were to remain on the same dose and regimen throughout the duration of the study. • For patients receiving sodium oxybate at study entry, documentation of prior improvement in cataplexy and EDS with sodium oxybate treatment was required.	• Narcolepsy secondary to another medical condition (eg, CNS injury or lesion) • Restless legs syndrome requiring treatment other than iron supplementation • Uncontrolled hyperthyroidism • History of seizures (other than early childhood febrile seizures) • Head trauma associated with loss of consciousness within the past 5 years • Clinically significant parasomnias • Untreated or inadequately treated sleep-disordered breathing, and succinic semialdehyde dehydrogenase deficiency • Major depression • History of psychotic disorders • Treatment with an antidepressant for cataplexy that could not be withdrawn if considered unsafe due to prior history of depression • Positive urine screen for benzodiazepines or drugs of abuse, a positive alcohol test, a history of substance abuse, or unwillingness to refrain from consuming alcohol during the study • Abnormal ECG
Primary Endpoint	**Secondary Endpoints**
• Change in weekly number of cataplexy attacks from the time during the 2 weeks of the stable-dose period to the time during the 2 weeks of the DB, RW period (determined from patient diaries)	• Change in ESS score from the end of the stable-dose period to the end of the DB, RW period • PGI-C • CGI-C • EQ-5D

- **Results:**
  - Efficacy was assessed in 134 patients who received randomized treatment, and safety was assessed in all enrolled patients (N = 201).
  - Enrolled patients were taking a variety of medications for the treatment of cataplexy at study entry: sodium oxybate only (n = 52), sodium oxybate + other anticataplectics (n = 23), other anticataplectics (n = 36), and cataplexy treatment-naïve (n = 90). During the stable-dose period, 38.8% of patients overall were on stimulants/wake-promoting agents, and the use of stimulants/wake-promoting agents was generally similar across participants by treatment at study entry (sodium oxybate only, 44.2%; sodium oxybate + other anticataplectic, 30.4%; non-sodium oxybate anticataplectic, 47.2%; cataplexy treatment-naïve, 36.7%).
  - Of the 201 patients enrolled, 155 completed the OL optimized treatment and titration period and 149 entered the stable-dose period. Discontinuations prior to the stable-dose period (n = 52) were attributed to AEs (n = 19), protocol deviations (n = 11), withdrawal by participant (n = 6), or other reasons (n = 2).
  - Overall, in the safety population, the mean age was 37.2 years and 60.7% of the participants were female. Prior to any narcolepsy treatment, all participants experienced cataplexy (100%) and EDS (100%), and the majority of participants reported experiencing other symptoms of the narcolepsy pentad: disrupted nighttime sleep (63.2%), sleep-related hallucinations (59.7%), and sleep paralysis (59.7%).
  - Prior to randomization, the median (Q1, Q3) number of weekly cataplexy attacks did not differ in patients randomized to placebo (1.1 [0.0, 7.9]) vs those who continued oxybate salts treatment (1.0 [0.0, 4.4]). During the DB, RW period, patients randomized to continue oxybate salts experienced no change (median [IQR], mean [SD]) in the weekly frequency of cataplexy attacks, while patients randomized to discontinue oxybate salts and take placebo experienced an increase in cataplexy attacks (median [Q1, Q3]: 0.0 [-0.5, 1.7], mean [SD]: 0.12 [5.77] vs 2.4 [0.0,11.6], mean [SD]: 11.46 [24.75], respectively; treatment difference, $p < 0.0001$) (Table 10).
  - Prior to randomization, the median (Q1, Q3) ESS score did not differ in oxybate salts-treated patients who were randomized to placebo vs those who continued oxybate salts treatment (13.0 [9.0, 17.0] vs 14.0 [10.0, 19.0],

respectively). At the end of the DB, RW period, the change in median (Q1, Q3) ESS score from baseline for patients randomized to placebo vs oxybate salts was 2.0 (0.0, 5.0) vs 0.0 (-1.0, 1.0), respectively (Table 10).

Table 10. Primary and key secondary endpoints (efficacy population)

Endpoint	Placebo (N = 65)	Oxybate salts (N = 69)
Change in weekly number of cataplexy attacks from SDP to DB, RW period (primary efficacy endpoint)		
Mean (SD)	11.46 (24.751)	0.12 (5.772)
Median	2.35	0.00
Q1, Q3	0.0, 11.61	-0.49, 1.75
Location shift*	-3.308	
95% CI†; p-value‡	-6.044 to -1.500; p < 0.0001	
Change in ESS score from SDP to DB, RW period (key secondary efficacy endpoint)		
Mean (SD)	3.0 (4.68)	0.0 (2.90)
Median	2.0	0.00
Q1, Q3	0.0, 5.0	-1.0, 1.0
Location shift*	0.0, 5.0	
95% CI‡; p-value‡	-4.00 to -1.00; p < 0.0001	

Abbreviation: SDP = stable dose period
*Location shift between 2 treatment groups and asymptotic 95% CI from Hodges-Lehmann estimate (sodium oxybate-placebo).
† From a rank-based ANCOVA model including the change in average weekly number of cataplexy attacks from the 2 weeks of the SDP to the 2 weeks of the DB, RW period as response variable, prior treatment group and study treatment group as fixed effects, and average weekly number of cataplexy attacks during the 2 weeks of the SDP as covariate.
‡ From a rank-based ANCOVA model including the change in ESS total score from the end of the SDP to the end of the DB, RW period as response variable, prior treatment group and study treatment group as fixed effects, and ESS total score at the end of the SDP as covariate.

- The distribution of PGI-C ratings for narcolepsy overall demonstrated that more patients randomized to placebo experienced worsening of symptoms compared with those randomized to continue oxybate salts treatment (nominal p < 0.0001), with a greater percentage of patients randomized to placebo rating their narcolepsy overall as “much worse” or “very much worse” compared with patients randomized to continue oxybate salts treatment (44.6 vs 4.3%; post hoc nominal p < 0.0001). Similarly, the distribution of CGI-C ratings for narcolepsy overall demonstrated worsening in more participants randomized to placebo (nominal p < 0.0001), with a greater percentage of patients randomized to placebo rated by clinicians as “much worse” or “very much worse” compared with the percentage of patients randomized to continue oxybate salts treatment (60.0 vs 5.9%, respectively; post hoc nominal p < 0.0001).
- At least 1 TEAE was reported by 76.1% of patients while receiving oxybate salts. The most common TEAEs were headache (20.4%), nausea (12.9%), and dizziness (10.4%). Worsening cataplexy was reported as a TEAE by 20 (10.0%) patients; 17 of the 20 patients experienced worsening cataplexy during the tapering of other anticataplectics, and 3 were cataplexy treatment-naïve at study entry. The most common TEAEs leading to discontinuation of oxybate salts during the main study were worsening cataplexy (7/201; 3.5%), nausea (3/201; 1.5%), and anxiety, depressed mood, depression, headache, and irritability (each 2/201; 1.0%). Serious AEs were reported by 6 patients during the main study, including 3 during the OL, optimized treatment and titration period, 1 during the stable-dose period, and 2 reported the day after 2 weeks of placebo treatment in the DB, RW period.

- **Conclusion:**
  - The efficacy of oxybate salts for the treatment of cataplexy and EDS in adults with narcolepsy was demonstrated in this PC, DB, RW study. The overall safety profile of oxybate salts was consistent with sodium oxybate.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - N/A (unpublished)
  - **Study strengths:**
    - Concomitant stimulant or wake-promoting agents were allowed, which could be considered more representative of real-world clinical practice, in which they are commonly prescribed in addition to sodium oxybate.
  - **Study limitations:**
    - The sample size was small.
    - Patients with mild cataplexy (< 14 attacks per 2-week period) were excluded.
    - Efficacy during the DB, RW period might have been underestimated because of the short duration (2 weeks).
    - The study was limited to patients with narcolepsy with cataplexy.

Solriamfetol

Narcolepsy/OSA

Study 18. Thorpy et al, *Ann Neurol.* 2019;85:359-370 (TONES 2)

Study Objective: Evaluate the safety and efficacy of solriamfetol for the treatment of narcolepsy	
Study Design, Follow-up	**Treatment Groups** (N = 239)
• 12-week, Phase 3, DB, PC, PG, MC, RCT • The study was performed at 50 study centers in the U.S. and Canada and 9 centers in Finland, France, Germany, and Italy. • Randomization was stratified on the basis of presence or absence of cataplexy.	• Solriamfetol 75 mg once daily (n = 59) • Solriamfetol 150 mg once daily (n = 55) • Solriamfetol 300 mg once daily (n = 59) • Placebo (n = 58) • Patients who were randomized to the 150 and 300 mg doses received 75 and 150 mg, respectively, on days 1 through 3 of the first week, with the full dose commencing on day 4.
Inclusion Criteria	**Exclusion Criteria**
• Adults, aged 18 to 75 years • Diagnosis of narcolepsy type 1 or type 2 according to the ICSD-3 or DSM-5 criteria ○ The DSM-5 criteria include patients who have been diagnosed with narcolepsy based on the presence of cataplexy and were applied in this study to include such patients who had been diagnosed with narcolepsy on the basis of cataplexy under ICSD-2 but who no longer meet diagnostic criteria based on a history of cataplexy under ICSD-3. • Baseline mean sleep latency < 25 minutes on the first 4 trials of a 5-trial, 40-minute MWT, baseline ESS score ≥ 10, usual nightly total sleep time ≥ 6 hours (by self-report), and a body mass index (BMI) between 18 and 45 kg/m^2	• Presence of any clinically relevant untreated medical, psychiatric, or behavioral disorder or medical condition other than narcolepsy that is associated with EDS (ie, night-time or variable shift work) • History or presence of any acutely unstable medical or psychiatric disorder, or surgical history that could affect the safety of the patient • Use of medications that could affect the evaluation of EDS or cataplexy unless prior use had stopped for > 5 half-lives of the drug and the patient had returned to baseline level of daytime sleepiness ≥ 7 days prior to the baseline visit.
Co-Primary Endpoints	**Secondary Endpoints**
• Change from baseline to week 12 in: ○ MWT mean sleep latency on the first 4 trials of the MWT ○ ESS score (see Appendix D)	• Percentage of patients who reported improvement on the PGI-C at week 12 • Change in sleep latency on each of the 5 MWT trials • Change in mean sleep latency from baseline to week 4 • Change in ESS from baseline to weeks 1, 4, and 8 • Percentage of patients who reported improvement on the PGI-C at weeks 1, 4, and 8 • Percentage of patients who reported improved at weeks 1, 4, 8, and 12 on the CGI-C • Change in the mean and median weekly number of cataplexy attacks was an exploratory endpoint among the subgroup of patients who reported the presence of cataplexy (assessed by patient diary).

- **Results:**
  - Demographic and clinical characteristics were similar across treatment groups.
  - Overall, the majority of patients (64.4%) were rated by clinicians as moderately or markedly ill and were characterized by impaired wakefulness and EDS, as indicated by baseline MWT mean sleep latency of 7.5 (SD = 5.7) min and ESS scores of 17.2 (SD = 3.2), respectively. Most patients (90.7%) had prior use of psychostimulants; prior use of sodium oxybate and antidepressants was reported for 25.8% and 34.7% of patients, respectively. Cataplexy was present in 50.8% of patients overall, with similar percentages of patients with cataplexy in each of the treatment groups.
  - The mITT population consisted of 231 patients; 1 patient randomized to placebo and 4 patients randomized to solriamfetol 150 mg did not have baseline or at least 1 post-baseline efficacy assessment of MWT and ESS.

- The discontinuation rate was highest in the solriamfetol 300 mg group (27.1%, with lack of efficacy [10.2%, n = 6] and AEs [8.5%, n = 5] as the most common reasons for discontinuation), followed by the solriamfetol 75 mg (16.9%), placebo (10.3%), and solriamfetol 150 mg (7.3%) groups.
- Solriamfetol 300 mg and 150 mg doses met the co-primary endpoints of MWT and ESS as well as the percentage of patients who reported improvement on the PGI-C (all $p < 0.0001$, Table 10). Significance was not achieved for the 75 mg dose on the MWT.
- The LS mean change from baseline at week 12 on the MWT showed an increase in mean sleep latency of 12.3 (SE = 1.4) and 9.8 (SE = 1.3) min with solriamfetol 300 mg and 150 mg, respectively, which was significant compared with 2.1 (SE = 1.3) min for placebo (both $p < 0.0001$).
- For the ESS score, the LS mean change from baseline at week 12 was -6.4 (SE = 0.7), -5.4 (SE = 0.7), and -3.8 (SE = 0.7) for the 300 mg, 150 mg, and 75 mg doses of solriamfetol, respectively, and -1.6 (SE = 0.7) with placebo.
- Improvements were observed at all solriamfetol doses at week 1 on the MWT. The magnitude of effect remained stable over the 12 weeks of the study, and the 300 and 150 mg doses differed from placebo at weeks 1 and 4. Similar patterns were observed on the ESS, with reductions in ESS score relative to placebo observed as early as week 1 with the 300 and 150 mg doses, and effects remained stable over the study duration.
- Evaluation of mean sleep latency on each of the 5 individual MWT trials at week 12 showed efficacy beginning at 1 hour after dosing through 9 hours after dosing for solriamfetol 150 and 300 mg.
- Solriamfetol increased the percentage of patients who reported improvement in their overall condition on the PGI-C. At week 12, these increases were dose-dependent and were significant for the solriamfetol 300 mg (84.7%) and 150 mg (78.2%) doses vs placebo (39.7%; both $p < 0.0001$); the 75 mg dose was nominally significant (67.8%) compared with placebo ($p = 0.0023$, but the comparison was below the hierarchical break). Effects were observed at all doses by week 1 and remained stable over the course of the study.
- On the CGI-C, all doses of solriamfetol resulted in higher percentages of patients who improved as early as week 1, with effects at 300 mg and 150 mg maintained over the study. The results of each of the sensitivity analyses across each of the endpoints (MWT, ESS, and PGI-C) yielded similar results and conclusions as the primary analyses of those endpoints.
- There was no clear effect of solriamfetol on the number of cataplexy attacks per week among patients with cataplexy, although this study was not powered or designed to rigorously evaluate the effects of solriamfetol on cataplexy (data not shown).

Table 11. Hierarchical testing of co-primary and key secondary efficacy endpoints in the mITT population

Endpoint	Solriamfetol treatment difference from placebo, LS mean (95% CI)		
	300 mg	150 mg	75 mg
MWT, min	10.14 (6.39 to 13.90) p < 0.0001	7.65 (3.99 to 11.31) p < 0.0001	2.62 (-1.04 to 6.28) p = 0.1595
ESS	-4.7 (-6.6 to -2.9) p < 0.0001	-3.8 (-5.6 to -2.0) p < 0.0001	-2.2 (-4.0 to -0.3) p = 0.0211
PGI-C, %	45.1 (29.51 to 60.67) p < 0.0001	38.5 (21.86 to 55.19) p < 0.0001	28.1 (10.80 to 45.48) p = 0.0023*

A fixed hierarchical testing procedure was used to correct for multiplicity, starting with the highest solriamfetol dose for the co-primary endpoints and followed by the key secondary endpoint; testing proceeded in that order for each subsequent lower dose, with statistical significance claimed only for those outcomes above the break in the hierarchy.
*Nominal p-value, because it is below the hierarchical break.

- Discontinuations due to AEs occurred in 8.5%, 5.1%, and 1.7% of the solriamfetol 300 mg, 150 mg, and placebo groups, respectively. Other than cataplexy, which resulted in discontinuation in 2 patients, none of the AEs leading to study discontinuation occurred in > 1 patient.
- AEs with an incidence ≥ 5% in the combined solriamfetol dose groups included headache (21.5%), nausea (10.7%), decreased appetite (10.7%), nasopharyngitis (9.0%), dry mouth (7.3%), and anxiety (5.1%).
- No patient had a TEAE of hypertension, and 2 patients had a TEAE of BP increase (1 in the 150 mg group and 1 in the 300 mg group).

- **Authors' conclusion:**
  - Once-daily oral dosing of solriamfetol 150 and 300 mg resulted in major improvements in wakefulness and reductions in EDS associated with narcolepsy together with patient- and clinician-reported global improvements. These results demonstrate that solriamfetol represents an important potential future therapeutic option for the treatment of impaired wakefulness and EDS in individuals with narcolepsy.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals

- **Study rating:**
  - Fair
- **Study strengths:**
  - The study used both objective and patient-reported validated outcome measures.
- **Study limitations:**
  - The trial had a short duration of 12 weeks.
  - Conclusions with regard to the effect of solriamfetol on cataplexy are limited by this study not being designed to rigorously evaluate effects on cataplexy. The frequency of type 2 narcolepsy (ie, without cataplexy) in approximately 50% of the study population was also somewhat higher than reported in the narcolepsy literature.
  - The study did not include modafinil or armodafinil as a comparator.

Study 19. Schweitzer et al, *Am J Respir Crit Care Med.* 2019; 199(11):1421-1431 (TONES 3)

Study Objective: Evaluate the safety and efficacy of solriamfetol for the treatment of EDS in patients with OSA with current or prior sleep apnea treatment	
Study Design, Follow-up	**Treatment Groups** (N = 476)
• 12-week, Phase 3, DB, PC, PG, MC, RCT • The study was conducted at 59 sites in the U.S., Canada, France, Germany, and the Netherlands • Randomization was stratified by adherence or non-adherence to primary OSA therapy, with adherence defined as use ≥ 4 hours per night on ≥ 70% of nights for devices from which hourly usage data could be extracted; use ≥ 70% of nights by daily diary for devices for which usage data could not be retrieved; or history of a surgical intervention for OSA. • Non-adherence was defined as usage of a primary therapy at a level that did not meet the above criteria, ie, non-use of a primary OSA therapy, or a history of a surgical intervention for OSA that was deemed by the investigator to no longer be effective at treating the obstruction.	• Solriamfetol 37.5 mg once daily (n = 58) • Solriamfetol 75 mg once daily (n = 62) • Solriamfetol 150 mg once daily (n = 117) • Solriamfetol 300 mg once daily (n = 118) • Placebo (n = 119) • Patients randomized to the 150 and 300 mg doses received 75 and 150 mg, respectively, on days 1 to 3, with the full dose commencing on day 4.
Inclusion Criteria	**Exclusion Criteria**
• Adults, aged 18 to 75 years • Diagnosis of OSA according to ICSD-3 criteria • Current or prior use of a primary OSA therapy including PAP, mandibular advancement device, or surgical intervention ○ Patients without current primary OSA therapy use or a history of a surgical intervention to treat the underlying obstruction were required to have tried to use a primary OSA therapy for at least 1 month with at least 1 documented adjustment to the therapy (eg, change in PAP pressure, change in mask, change in modality). • Baseline ESS score ≥ 10 • Baseline sleep latency < 30 min for the average of the first 4 of a 5-trial, 40-min MWT • Usual nightly sleep time of ≥ 6 hours	• Usual bedtime later than 1:00 AM • Occupation requiring nighttime shift work or variable shift work • Use of any OTC or prescription medications that could affect the evaluation of EDS; current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria • Nicotine dependence that has an effect on sleep (eg, a patient who routinely awakens at night to smoke) • Any other clinically relevant medical, behavioral, or psychiatric disorder other than OSA that is associated with excessive sleepiness
Co-Primary Endpoints	**Secondary Endpoints**

• Change from baseline to week 12 in:
  ○ Mean sleep latency derived from the first 4 trials of a 5-trial, 40-min MWT
  ○ ESS score
	• Change from baseline to week 12 in sleep latency for each of the 5 individual MWT trials was tested as a pre-specified secondary endpoint for doses that were positive on both co-primary efficacy endpoints
	• Percentage of patients reporting any improvement in PGI-C at week 12

	• Percentage of patients reporting any improvement in CGI-C at week 12

- **Results:**
  - Of the 474 patients who were randomized and took at least 1 dose of study drug, representing the safety population, 404 (85.2%) completed the study.
  - Baseline demographic and clinical characteristics of the safety population were similar across treatments.
  - A history of a surgical intervention for OSA was reported in 17.6% and 13.5% of patients on placebo and solriamfetol, respectively. At baseline, primary OSA therapy was used by 69.7% of patients on placebo and 73.5% of patients on solriamfetol; of these patients, 91.6% on placebo and 92.7% on solriamfetol were using PAP, 2.4% on placebo and 1.1% on solriamfetol were using another type of device as a primary OSA therapy, and in 6.0% of patients on placebo and 6.1% on solriamfetol, the type of primary OSA therapy was not specified.
  - In the 5 treatment groups, from 69.0 to 72.9% of patients were adherent to primary OSA therapy at baseline and from 27.1 to 31.6% were non-adherent.
  - AEs were the most common reason overall for withdrawal (5.1%).
  - Those who successfully completed at least 1 follow-up visit (mITT population) comprised 459 participants.
  - Mean treatment compliance with study drug was 97.2%.
  - The co-primary endpoints of change from baseline at week 12 in MWT and ESS were met at all solriamfetol doses, and the key secondary endpoint of PGI-C was met at all doses except the 37.5 mg dose (Table 12).
    - Solriamfetol resulted in dose-dependent increases in MWT sleep latency at week 1, with LS mean changes from baseline that ranged from 4.2 to 13.3 min for the 37.5 and 300 mg doses, respectively, and that were > placebo (0.4 min). These increases were maintained across the 12 weeks of the study, and all solriamfetol doses resulted in improvements relative to placebo at weeks 4 and 12 ($p < 0.05$). At week 12, effect sizes (Cohen's d) were 0.4, 0.9, 1.1 and 1.2 for solriamfetol 37.5, 75, 150, and 300 mg, respectively. The LS mean change from baseline exceeded 10 min at all time points with solriamfetol 150 mg (11.0 to 12.2 min) and 300 mg (13.0 to 13.8 min), whereas placebo ranged from 0.2 to 1.2 min.
  - Solriamfetol treatment resulted in dose-dependent decreases in ESS score relative to placebo at week 1 that remained stable over the 12-week study duration. These decreases were greater than placebo for all doses at all time points except for the 37.5 mg dose at week 8. Effect sizes at week 12 were 0.4, 0.4, 1.0, and 1.0 for solriamfetol 37.5, 75, 150, and 300 mg, respectively. ESS scores decreased by > 7 points with the 150 and 300 mg doses at week 12 ($p < 0.0001$), whereas placebo decreased by 3.3 points.
  - Change from baseline in sleep latency on each of the 5 individual MWT trials at week 12 was significantly greater with solriamfetol 75, 150, and 300 mg doses compared with placebo, demonstrating efficacy of solriamfetol from 1 to 9 hours after dosing. The 37.5 mg dose showed a significant difference relative to placebo for trial 2 only, based on the pre-specified testing sequence.
  - At week 12, significantly higher percentages of patients on solriamfetol 75 mg (72.4%; $p < 0.05$), 150 mg (89.7%; $p < 0.0001$), and 300 mg (88.7%; $p < 0.0001$) reported overall improvement on the PGI-C relative to placebo (49.1%). These effects were dose-dependent and apparent as early as week 1. Results were generally similar on the CGI-C.
  - There were no meaningful differences in response to solriamfetol between the subgroups of patients who were adherent or non-adherent to primary OSA therapy (data not shown).

Table 12. Hierarchical testing at week 12 of co-primary and key secondary endpoints in the mITT population*

Endpoint	Difference from placebo (95% CI); p-value			
	300 mg	150 mg	75 mg	37.5 mg
MWT, LS mean difference	12.8 (10.0 to 15.6); < 0.0001	10.7 (8.1 to 13.4); < 0.0001	8.9 (5.6 to 12.1); < 0.0001	4.5 (1.2 to 7.9); 0.0086
ESS, LS mean difference	-4.7 (-5.9 to -3.4); < 0.0001	-4.5 (-5.7 to -3.2); < 0.0001	-1.7 (-3.2 to -0.2); 0.0233	-1.9 (-3.4 to -0.3); 0.0161
PGI-C, % difference	39.6 (28.7, to 50.4); < 0.0001	40.5 (29.8 to 51.3); < 0.0001	23.3 (8.6 to 38.0); 0.0035	6.2 (-9.7 to 22.2); 0.4447

*A fixed hierarchical testing procedure was used to correct for multiplicity, starting with the highest solriamfetol dose for the co-primary endpoints and followed by the key secondary endpoint; testing proceeded in that order for each subsequent lower dose, with statistical significance claimed only for those outcomes above the break in the hierarchy.

  - A higher percentage of participants (7.3%) receiving solriamfetol withdrew due to AEs compared with placebo (3.4%). AEs leading to study discontinuation in ≥ 3 patients who received solriamfetol were anxiety (n = 4), feeling jittery (n = 4), nausea (n = 3), dizziness (n = 3), and chest discomfort (n = 3).
  - In most patients, AEs were of mild or moderate severity in the placebo (93.0%) and solriamfetol (94.6%) groups.

- The most frequently reported AEs with solriamfetol, defined as occurring in ≥ 5% of participants in any treatment group, included headache (10.1%), nausea (7.9%), decreased appetite (7.6%), anxiety (7.0%), and nasopharyngitis (5.1%); most of these AEs were dose-dependent.
- Insomnia was reported in 2 patients receiving placebo (1.7%), and in 1 (1.7%), 0 (0%), 3 (2.6%), and 11 (9.3%) participants receiving solriamfetol 37.5, 75, 150, and 300 mg, respectively.
- At week 12, vital signs taken at 7 time points during the day from pre-dose to 9 hours post-dose showed small mean (95% CI) increases from baseline in BP, with the highest at the 300 mg dose of solriamfetol (2.5 [95% CI, 0.4 to 4.6] and 1.5 [0.3 to 2.7] mm Hg for systolic and diastolic, respectively) relative to minimal changes with placebo (-0.2 [95% CI, -1.7 to 1.4] mm Hg systolic; 0.0 [95% CI, -0.9 to 1.0] mm Hg diastolic). Small dose-dependent mean effects were observed on heart rate with solriamfetol 150 and 300 mg (increases of 2.2 [95% CI, 1.0 to 3.4] and 2.9 [95% CI, 1.7 to 4.1] bpm, respectively, relative to 0.1 [95% CI, -0.9 to 1.1] bpm with placebo). No apparent effects of solriamfetol on BP or heart rate were observed on predose vital sign measures at week 12.

- **Authors' conclusion:**
  - Solriamfetol 75, 150, and 300 mg resulted in objective improvements in wakefulness, subjective improvements in sleepiness, and global improvements as evaluated by participants and clinicians. The safety and tolerability profile was consistent with prior studies of solriamfetol in individuals with narcolepsy, and similar to other wake-promoting agents used in the treatment of EDS in OSA.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - The study used both objective and patient-reported validated outcome measures.
    - Participants who were non-adherent to OSA therapy were included in order to study a population more representative of OSA patients in the clinical setting.
  - **Study limitations:**
    - The trial had a short duration of 12 weeks and did not assess longer-term outcomes related to safety and efficacy, including potential long-term CV consequences.
    - The study did not include modafinil or armodafinil as a comparator.

Study 20. Strollo et al, *Chest.* 2019; 155(2):364-374 (TONES 4)

Study Objective: Evaluate the maintenance of efficacy and safety of solriamfetol vs placebo for the treatment of EDS in adults with OSA	
Study Design, Follow-up	**Treatment Groups** (N = 124)
• Phase 3, DB, PC, PG, MC, RW study • After 2 weeks of clinical titration (n = 174, 75 mg once daily starting dose, titrated up or down every 3 days to 75, 150, or 300 mg) and 2 weeks of stable dose administration (n = 148), patients who reported much or very much improvement on the PGI-C and had numerical improvements on the MWT and ESS were randomly assigned to placebo or solriamfetol for 2 additional weeks. • Randomization was stratified by patients' adherence or non-adherence to a primary OSA therapy	• Solriamfetol once daily (n = 62) • Placebo (n = 62)
Inclusion Criteria	**Exclusion Criteria**
• Adults, aged 18 to 75 years • Diagnosis of OSA according to ICSD-3 criteria • Current or primary OSA therapy including CPAP, oral appliance, or surgical intervention • BMI 18 to < 45 kg/m^2 • Baseline ESS score ≥ 10 • Mean sleep latency < 30 minutes on the first 4 trials of a 5-trial, 40-min MWT • Usual nightly sleep time ≥ 6 hours	• Any disorder other than OSA associated with EDS • An occupation requiring nighttime shift work or variable shift work • Excessive caffeine use 1 week prior to the study or nicotine dependence with a reported effect on sleep • Presence of any acutely unstable medical condition, behavioral or psychiatric disorder, or surgical history that could affect patient safety or interfere with study assessments

	• Use of any OTC or prescription medications that could affect EDS evaluation within a period corresponding to at least 5 half-lives of the drug
Co-Primary Endpoints	**Secondary Endpoints**
• Changes from week 4 to week 6 in: ○ MWT mean sleep latency ○ ESS score	• Percentage of patients who reported worsening of their condition on the PGI-C from week 4 to week 6 • Percentage of patients who reported worsening of their condition on the CGI-C from week 4 to week 6 • FOSQ-10

- **Results:**
  - Of 174 patients enrolled into the titration phase, 71% (n = 124) were randomly assigned to placebo or solriamfetol in the DB RW phase. There were 17 study discontinuations (10%) during the titration phase, 6 of which were due to AEs. During the stable dose phase (n = 157), 9 patients (6%) discontinued, and 24 did not enter the RW phase, of whom 21 (13%) were for not meeting the criteria for improvement. Two patients randomly assigned to solriamfetol discontinued during the RW phase; the final mITT population consisted of 62 patients randomly assigned to placebo and 60 to solriamfetol.
  - In the stable dose phase, 14.6%, 31.8%, and 53.5% of patients received the 75, 150, and 300 mg doses of solriamfetol, respectively. Of the 62 patients randomly assigned to solriamfetol in the RW phase, 14.5%, 41.9%, and 43.5% received 75, 150, and 300 mg, respectively.
  - Analyses were performed on the mITT population, defined as patients who were randomly assigned who received ≥ 1 dose of study medication and who had an MWT or ESS assessment at week 4 and ≥ 1 assessment after week 4.
  - Baseline characteristics of the safety population (patients who received ≥ 1 dose of solriamfetol in the titration phase) and the mITT population were comparable between groups.
  - In the titration phase, 65.5% of patients were classified as moderately or markedly ill by their physicians on the CGI-C, 61.5% were male with a mean BMI of 33.3 kg/m^2, and 71.3% were using a primary OSA therapy at baseline.
  - In the mITT population, from baseline to week 4, mean MWT sleep latencies improved from 12.3 to 13.1 min to 29.0 to 31.7 min, and ESS scores improved from 15.3 to 16.0 to 5.9 to 6.4. Patient-reported EDS decreased from ~15 to 16 to ~6, which is within the normal range.
  - From weeks 4 to 6 (RW phase), solriamfetol-treated patients maintained improvements in MWT and ESS. The LS mean (SE) change in MWT mean sleep latency was -12.1 (1.3) min with placebo compared with -1.0 (1.4) min with solriamfetol; LS mean difference between solriamfetol and placebo was 11.2 minutes (95% CI, 7.8 to14.6; p < 0.0001). The LS mean changes in ESS scores were 4.5 (0.7) and -0.1 (0.7) for placebo and solriamfetol, respectively, resulting in an LS mean difference of -4.6 (95% CI, -6.4 to -2.8; p < 0.0001).
    - MWT and ESS results were similar in the subgroups of patients who were adherent or non-adherent with a primary OSA therapy, with slightly larger MD in the non-adherent subgroup.
  - During the RW phase, a statistically significant 50.0% of patients who were switched to placebo reported worsening on the PGI-C relative to 20.0% who continued using solriamfetol (-30.0; 95% CI, -46.0 to -14.0; p < 0.001). Similarly, 59.0% of patients switched to placebo worsened, as rated by the physicians on the CGI-C, vs 21.7% who continued using solriamfetol (-37.3; 95% CI, -53.50 to -21.19; p < 0.0001).
    - Results on the PGI-C and CGI-C were similar in the subgroups of patients who were adherent or non-adherent with a primary OSA therapy, with slightly larger differences from placebo in the non-adherent subgroup.
  - The FOSQ total score improved from mean baseline scores of 13.5 to 13.7 to mean scores of 17.6 to 17.8 after 4 weeks of treatment. At the end of the RW phase (week 6), mean ±SD FOSQ-10 scores were 16.4 ± 2.9 in the placebo group and 17.4 ± 3.0 with solriamfetol, resulting in LS mean (SE) changes of -1.3 (0.4) and -0.2 (0.4), respectively; the LS mean difference significantly favored solriamfetol (1.2; 95% CI, 0.2 to 2.1; p < 0.05).
  - There were no serious AEs during the study, and all withdrawals due to AEs (3.4%, n = 6) occurred during the titration phase. The most frequent AEs leading to withdrawal were headache and palpitations (each reported for 2 patients). There was a higher incidence of AEs during the titration phase (48.9%) than during the stable dose phase (10.2%) and the incidence of AEs increased by dose. The most common AEs (≥ 5%) during the titration phase included headache, (9.8%), dry mouth (6.9%), nausea (6.9%), dizziness (5.7%), and insomnia (5.7%) and the incidence of these AEs (0.6 to 1.3%) was lower during the stable dose phase.
  - During the RW phase, 29.0% of patients who continued using solriamfetol experienced any AE relative to 9.7% of those switched to placebo. Nasopharyngitis was the most frequent AE (4.8%), and there was no evidence of rebound hypersomnia or withdrawal effects after abrupt discontinuation of solriamfetol in the placebo group.
  - The mean changes in vital signs obtained before administration of the dose to 9 hours after administration of the dose on MWT days, across solriamfetol doses, were small increases from baseline to week 6 in systolic (mean ±SD change of 1.6 ± 8.7 mm Hg) and diastolic (0.8 ± 5.3 mm Hg) BP, as well as heart rate (1.0 ± 6.1 bpm). In the RW

phase, small changes in BP (1.5 ± 7.6 mm Hg for systolic and 0.5 ± 4.3 mm Hg for diastolic) and heart rate (0.2 ± 5.9 bpm) were observed in patients randomly assigned to placebo.

- **Authors' conclusion:**
  - Solriamfetol substantially increased objective wakefulness and decreased subjective EDS, with effects that were maintained in participants who continued using treatment relative to a loss of efficacy among those randomly assigned to placebo. The safety profile was consistent with those of other solriamfetol studies, and abrupt discontinuation was not associated with rebound hypersomnia or withdrawal effects.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - N/A (RW study)
  - **Study strengths:**
    - Inclusion of non-adherent patients in the study likely reflects the characteristics of the general population of patients with OSA who may benefit from solriamfetol treatment.
  - **Study limitations:**
    - The study had a small sample size.
    - The study had a short duration.
    - The inclusion of a population enriched for treatment response, which, although customary for the RW study design, limits characterization of solriamfetol treatment effects in individuals who did not meet response criteria for random assignment.
    - Approximately 20 to 30% of patients were not using a primary OSA therapy at evaluated time points, which may have caused heterogeneity in treatment response.

Study 21. Malhotra et al, *Sleep*. 2020;43(2); Sunosi dossier 2019 (TONES 5)

Study Objective: Evaluate the long-term safety and maintenance of efficacy of solriamfetol for up to 52 weeks in the treatment of patients with narcolepsy or OSA who completed previous trials of solriamfetol	
Study Design, Follow-up	**Treatment Group**
• Phase 3, OL extension study • A 2-week titration phase was followed by a maintenance phase of up to 50 weeks. After ~6 months of OL treatment with solriamfetol, a subgroup of patients entered a 2-week PC RW phase, and the maintenance phase was resumed after RW phase completion.	• Solriamfetol (Group A, n = 519; Group B, n = 124) • Due to differences in study design as well as variable duration between prior study completion and enrollment in the long-term study, participants were enrolled into one of 2 groups. Group A included participants who completed a Phase 3, 12-week narcolepsy or OSA study, and who immediately enrolled into this long-term study; the study duration in this group was 40 weeks. Group B included participants with narcolepsy or OSA who completed one of the Phase 2 studies (or the 6-week, Phase 3 study and were subsequently enrolled into this long-term study. These participants had a study duration for 52 weeks. • During the 2-week titration phase, participants began with a once-daily dose of 75 mg and could titrate up 1 dose level every 3 days (to 150 mg/d and then a maximum dose of 300 mg/d). Participants were also able to titrate down to 75 or 150 mg at any time. • During the RW phase, patients were randomized either to placebo or to continue solriamfetol at their dose of 75 mg, 150 mg, or 300 mg for 2 weeks. • At the end of the RW phase and for the remainder of the study, participants resumed solriamfetol treatment at the same dose that they had received at the beginning of the RW phase.
Inclusion Criteria	**Exclusion Criteria**
• Patients with narcolepsy or OSA who had completed a prior Phase 2 or Phase 3 study with solriamfetol	• See above parent study descriptions
Primary Endpoint	**Secondary Endpoints**

• Change in ESS score from the beginning to the end of the 2-week RW phase	• PGI-C • CGI-C

- **Results:**
  - The overall safety population in the OL phase consisted of 643 patients (417 [64.9%] with OSA and 226 [35.1%] with narcolepsy). A total of 458 (71%) patients completed the study including 66.4% of narcolepsy participants and 73.9% of OSA participants. Patients were primarily male (52.4%) and White (78.7%), with a mean age of 49.3 years. Comorbid conditions included HTN (37.6%), hyperlipidemia (15.2%), and type 2 diabetes (14.0%). The percentages of participants who were titrated to 75, 150, and 300 mg were 10.0%, 32.2%, and 57.9%, respectively. A total of 282 patients were randomized into the RW phase, of which 280 completed this phase. One hundred-forty-one received placebo and 139 received solriamfetol, which represented the mITT population.
  - At study baseline, primary OSA therapy was used by 71.5% of OSA participants; of these participants, 93.2% were using PAP at entry into this study, 2.3% were using another type of device as a primary OSA therapy (eg, neurostimulator or mandibular advancement device), and 5.4% did not specify the type of primary OSA therapy.
  - Efficacy during the maintenance phase
    - In the overall population, mean ESS scores were 15.9 for group A and 16.2 for group B at baseline of the parent and current study, respectively. At week 2, mean ESS scores decreased to 7.6 for group A and to 7.8 for group B, and these improvements (ie, decrease in mean ESS scores) were maintained throughout the study duration. Similar patterns were observed in the individual narcolepsy and OSA populations.
    - The majority of participants (> 94%) reported improvements on the PGI-C at week 2, and these improvements were maintained at generally similar percentages at each assessment; 87.1 to 90.4% of participants in group A and 86.8 to 96.4% of participants in group B reported improvement on the PGI-C at the final assessment. Sustained improvements from the first assessment at week 2 over the study duration were also reported from the clinician perspective on the CGI-C, with good concordance with the PGI-C for the percentage of participants who improved. Similar patterns were observed in the individual narcolepsy and OSA populations.
  - Efficacy during the RW phase
    - All primary and secondary endpoints were met for the RW phase ($p < 0.0001$) in the mITT population. Participants who received solriamfetol during the RW phase maintained their improvement from the beginning of the RW phase, whereas those who were randomized to receive placebo worsened. The LS mean change (from the beginning to the end of the RW phase) for the ESS score was 1.6 with solriamfetol compared with 5.3 with placebo, resulting in an LS mean difference of -3.7 (95% CI, -4.80 to -2.65; $p < 0.0001$. In the overall population, significantly greater percentages of participants in the placebo group worsened during the RW phase compared with the solriamfetol group on both the PGI-C (64.5% vs 28.2%; $p < 0.0001$) and CGI-C (63.8% vs 28.7%; $p < 0.0001$). Similar results were observed by indication across endpoints ($p < 0.05$; data not shown).
  - Over the study duration, 482 participants (75%) had at least 1 TEAE, with similar percentages among those with narcolepsy (74.8%) and OSA (75.1%); 44% of participants (283/643) had a TEAE within the first 2 weeks whereas 12.8% had a TEAE during the second 2 weeks of treatment.
  - The most frequent TEAEs (≥ 5% in combined solriamfetol groups for any indication) were headache (11%), nausea (8.9%), insomnia (7.9%), nasopharyngitis (8.4%), dry mouth (7.3%), anxiety (7.2%), decreased appetite (5.0%), and upper respiratory tract infection (5.0%); most TEAEs were mild or moderate. With the exception of sinusitis, nasopharyngitis, and upper respiratory tract infection, the most common TEAEs occurred most often during the first 2 weeks of the study. TEAE profiles were similar in participants with OSA and narcolepsy. During the OL period, 59 (9.2%) participants had TEAEs that led to withdrawal from the study. TEAEs leading to withdrawal most frequently occurred in the system organ classes of psychiatric disorders (n = 20; 3.1%), nervous system disorders (n = 13; 2.0%), and gastrointestinal disorders (n = 8; 1.2%).TEAEs that most frequently led to withdrawal were anxiety (*n* = 7; 1.1%), headache (n = 4; 0.6%), insomnia (n = 4; 0.6%), irritability (n = 4; 0.6%), nausea (n = 4; 0.6%), depression (n = 3; 0.3%), and dry mouth (n = 3; 0.3%).
  - Serious TEAEs were reported in 27 patients (4.2%) across all phases, including 21 participants (5.0%) with OSA and 6 participants (2.7%) with narcolepsy. There was 1 death that was considered unrelated to study drug. A total of 9 participants, all with OSA, had CV or potential CV serious TEAEs: 2 participants with atrial fibrillation; 1 each with angina pectoris, chest discomfort, chest pain, noncardiac chest pain, cerebrovascular accident, pulmonary embolism; and 1 patient with acute myocardial infarction discussed previously. Of these serious TEAEs, 2 were deemed by the investigator to be related to study drug administration: atrial fibrillation in a patient whose concomitant medications included 2 types of thyroid medication, and cerebrovascular accident in a patient with a history of HTN.
  - Rebound hypersomnia, as assessed by changes on the ESS, was not observed after abrupt discontinuation of solriamfetol in the RW phase.
  - There was no pattern of withdrawal signs or symptoms based on analysis of AEs that occurred after abrupt discontinuation of long-term exposure to solriamfetol (ie, the placebo group in the RW phase).

- No clinically relevant changes in heart rate (< 1 beat per minute [bpm]) or blood pressure (< 1 mm Hg) were observed at assessed time points in group A (n = 519). However, for group B (n = 124), mean increases from baseline ranged from 1.0 to 4.3 mm Hg for systolic blood pressure, 0.8 to 2.4 mm Hg for diastolic blood pressure, and 0.6 to 4.2 bpm for heart rate across the OL extension (up to 52 weeks); these increases were generally greater for participants with narcolepsy relative to OSA. No apparent trends were observed to suggest that there were long-term increases (ie, worsening) in heart rate or blood pressure over time for participants with narcolepsy or OSA (in both group A and group B).

- **Authors' Conclusion:**
  - The long-term maintenance of efficacy with solriamfetol was demonstrated for the treatment of EDS in patients with narcolepsy or OSA. During the maintenance phase, improvements with solriamfetol were maintained for up to 1 year. The safety profile was consistent with prior PC studies of solriamfetol and there were no safety concerns that emerged with chronic administration of up to 1 year.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - N/A (OL extension study)
  - **Study strengths:**
    - The study had a large sample size.
    - The study included patients with narcolepsy with and without cataplexy.
    - The study followed patients for up to 1 year.
  - **Study limitations:**
    - There was no placebo group for comparison, nor was solriamfetol compared with other wake-promoting agents.
    - The study did not focus on objective outcome measures such as the MWT, neurocognitive performance, or motor vehicle accident risk due to EDS but rather patient-reported outcomes.

CLINICAL GUIDELINES

AASM practice parameters for the treatment of narcolepsy and other hypersomnias of central origin (*Morgenthaler et al 2007a*) (see Appendix H for grading of evidence definitions)

- Recommendations for treatment of narcolepsy:
  - Most of the agents used to treat excessive sleepiness have little effect on cataplexy or other REM sleep associated symptoms. Conversely, most antidepressants and anticataplectics have little effect on alertness. However, some compounds act on both symptoms. Compounds should be selected depending on the diagnosis and the targeted symptoms. Co-administration of 2 or more classes of compounds may be needed in some patients to adequately address their symptoms.
  - Modafinil is effective for treatment of daytime sleepiness due to narcolepsy (Standard).
  - Sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy (Standard). Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis (Option).
  - Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy (Guideline).
  - Selegiline may be an effective treatment for cataplexy and daytime sleepiness (Option).
  - Ritanserin (not available in the U.S.) may be effective treatment of daytime sleepiness due to narcolepsy (Option).
  - Scheduled naps can be beneficial to combat sleepiness but seldom suffice as primary therapy for narcolepsy (Guideline).
  - TCAs, SSRIs, venlafaxine, and reboxetine (not available in the U.S.) may be effective treatment for cataplexy (Guideline).
  - TCAs, SSRIs, and venlafaxine may be effective treatment for treatment of sleep paralysis and hypnagogic hallucinations (Option).

AASM practice parameters for the medical therapy of OSA (*Morgenthaler et al 2006*)

- Recommendations for pharmacologic therapy of OSA:
  - Successful dietary weight loss may improve the AHI in obese OSA patients (Guideline).
  - Dietary weight loss should be combined with a primary treatment for OSA (Option).
  - Bariatric surgery may be adjunctive in the treatment of OSA in obese patients (Option).
  - SSRIs are not recommended for treatment of OSA (Standard).
  - Protriptyline is not recommended as a primary treatment for OSA (Guideline).
  - Methylxanthine derivatives (aminophylline and theophylline) are not recommended for treatment of OSA (Standard).

- Estrogen therapy (estrogen preparations with or without progesterone) is not indicated for the treatment of OSA (Standard).
- Modafinil is recommended for the treatment of residual EDS in OSA patients who have sleepiness despite effective PAP treatment and who are lacking any other identifiable cause for their sleepiness (Standard).

AASM practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders (*Morgenthaler et al 2007b*)

- Recommendations for SWD:
  - Planned napping before or during the night shift is indicated to improve alertness and performance among night shift workers (Standard).
  - Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work (Guideline).
  - Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers (Guideline).
  - Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered (Guideline).
  - Modafinil is indicated to enhance alertness during the night shift for SWD (Guideline).
  - Caffeine is indicated to enhance alertness during the night shift for SWD (Option).

EAN. Management of narcolepsy in adults (*Billiard et al 2011)* (see Appendix I for grading of evidence definitions)

- Recommendations for treatment of narcolepsy:
  - EDS and sleep attacks:
    - The first-line pharmacological treatment of EDS and sleep attacks is not unequivocal. When EDS is the most disturbing symptom, modafinil is recommended based on its efficacy, limited AEs, and dosing flexibility. Modafinil can be taken in variable doses from 100 to 400 mg/day, given as 1 dose in the morning or 2 doses, 1 in the morning and 1 early in the afternoon or tailored to individual patient needs.
    - When EDS coexists with cataplexy and poor sleep, sodium oxybate may be given, based on its well-evidenced efficacy on the 3 symptoms. However, this benefit should be balanced with its more delicate manipulation: the dose should be carefully titrated up to an adequate level over several weeks; the drug should not be used in combination with other sedatives, respiratory depressants and muscle relaxants; patient should be monitored for development of sleep-disordered breathing; and its use should be avoided in depressed patients. Sodium oxybate should be given at a starting dose of 4.5 g/night, increasing by increments of 1.5 g at 4-week intervals. AEs may require dose reduction and slow titration. The optimal response on EDS may take as long as 8 to 12 weeks. Supplementation with modafinil is generally more successful than sodium oxybate alone.
    - Methylphenidate may be an option when the response to modafinil is inadequate and sodium oxybate is not recommended. Moreover, the short-acting effect of methylphenidate may be beneficial when modafinil needs to be supplemented at a specific time of the day, or in situations where maximum alertness is required. Methylphenidate LP and mazindol (not available in the U.S.) may be useful in a limited number of cases.
    - Behavioral treatment measures are always advisable. Essentially, the studies available support on a B Level the recommendation to have regular nocturnal sleep times and to take planned naps during the day, as naps temporarily decrease sleep tendency and shorten reaction time. Because of varying performance demands and limitations on work or home times for taking them, naps are best scheduled on a patient-by-patient basis.
  - Cataplexy:
    - Based on several Class I evidence (Level A rating) studies, sodium oxybate is recommended for first-line pharmacological treatment of cataplexy at a starting dose of 4.5 g/night divided into 2 equal doses of 2.25 g/night. The dose may be increased to a maximum of 9 g/night, divided into 2 equal doses of 4.5 g/night, by increments of 1.5 g at 2-week intervals. Special considerations are noted above.
    - Second-line pharmacological treatments are antidepressants. TCAs, particularly clomipramine (10 to 75 mg), are potent anticataplectic drugs. However, they have the disadvantage of anticholinergic AEs. The starting dosage should always be as low as possible. SSRIs are slightly less active but have fewer AEs. The norepinephrine/serotonin reuptake inhibitor venlafaxine is widely used but lacks any published clinical evidence of efficacy. The norepinephrine reuptake inhibitors, such as reboxetine and atomoxetine, also lack published clinical evidence. Given the well-evidenced efficacy of sodium oxybate and antidepressants, the place for other compounds is fairly limited. There is no accepted behavioral treatment of cataplexy.
  - Hallucinations and sleep paralysis:
    - Recommendations are the same as for cataplexy.
  - Poor sleep:

- According to recent studies with sodium oxybate, this agent appears as the most appropriate to treat poor sleep (Level A). Benzodiazepine or non-benzodiazepine hypnotics may be effective in consolidating nocturnal sleep (Level C). Unfortunately, objective evidence is lacking over intermediate or long-term follow-up. The improvement in poor sleep reported by some patients once established on modafinil is noteworthy.

- Associated features:
  - OSA/hypopnea should be treated no differently in narcoleptic patients than the general population, although it has been shown that CPAP does not improve EDS in most narcolepsy patients. There is usually no need to treat PLMS in narcoleptic patients. Antidepressants and psychotherapy should be used in depressed narcoleptic patients (Level C) as in non-narcoleptic depressed patients.

SAFETY

- **Contraindications**
  - Armodafinil/modafinil
    - Known hypersensitivity to armodafinil or modafinil or its inactive ingredients
  - Pitolisant
    - Patients with severe hepatic impairment
      - Pitolisant is extensively metabolized by the liver and there is a significant increase in pitolisant exposure in patients with moderate hepatic impairment.
  - Solriamfetol
    - Concomitant use of MAOIs, or within 14 days following discontinuation of an MAOI because of the risk of hypertensive reaction
  - Sodium oxybate/oxybate salts
    - Concomitant use of sedative hypnotic agents
    - Concomitant use of alcohol
    - Diagnosis of semialdehyde dehydrogenase deficiency, a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.
- **Warnings/precautions**
  - Armodafinil/modafinil
    - *Serious dermatologic reactions, including SJS and TEN*
      - Serious rash requiring hospitalization and discontinuation of treatment has been reported in association with the use of modafinil/armodafinil.
      - Rare cases of SJS and TEN have been reported in adults and children in worldwide postmarketing experience with armodafinil/modafinil.
      - There are no factors known to predict the risk of occurrence or the severity of rash associated with armodafinil/modafinil.
      - In cases where the time to onset was reported, serious rash occurred 1 day to 2 months after initiation of armodafinil. Nearly all cases of serious rash associated with modafinil occurred within 1 to 5 weeks after treatment initiation. However, isolated cases with either drug have been reported after prolonged treatment (eg, 3 months).
    - *DRESS/multiorgan hypersensitivity*
      - One fatal case of DRESS (also known as multiorgan hypersensitivity) that occurred in close temporal association (3 weeks) with the initiation of armodafinil treatment has been reported in the postmarketing setting. DRESS typically presents with fever, rash, lymphadenopathy, and/or facial swelling in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. In addition, multiorgan hypersensitivity reactions, including at least 1 fatality in postmarketing experience, have occurred in close temporal association (median time to detection 13 days; range, 4 to 33) to the initiation of modafinil. Although there have been a limited number of reports, multiorgan hypersensitivity reactions may result in hospitalization or be life-threatening.
    - *Angioedema and anaphylaxis reactions*
      - Angioedema and hypersensitivity (with rash, dysphagia, and bronchospasm) were observed in patients treated with armodafinil. No such cases were observed in modafinil clinical trials. However, angioedema has been reported in postmarketing experience with modafinil. Patients should be advised to discontinue therapy and immediately report to their physician any signs or symptoms suggesting angioedema or anaphylaxis (eg, swelling of face, eyes, lips, tongue or larynx; difficulty in swallowing or breathing; hoarseness).
    - *Persistent sleepiness*
      - Patients with abnormal levels of sleepiness who take modafinil/armodafinil should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking modafinil/armodafinil, should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity. Prescribers should also be aware that

patients may not acknowledge sleepiness or drowsiness until directly questioned about drowsiness or sleepiness during specific activities.

- *Psychiatric symptoms*
  - Psychiatric AEs have been reported in association with the use of modafinil/armodafinil.
  - Postmarketing AEs associated with the use of modafinil/armodafinil, some of which have resulted in hospitalization, have included mania, delusions, hallucinations, suicidal ideation, and aggression. Many, but not all, patients who developed psychiatric AEs had a prior psychiatric history.
- *Known CV disease*
  - In clinical studies of modafinil, CV AEs, including chest pain, palpitations, dyspnea and transient ischemic T-wave changes on ECG were observed in 3 patients in association with mitral valve prolapse or left ventricular hypertrophy. Use of modafinil/armodafinil is not recommended in patients with a history of left ventricular hypertrophy or in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants.

○ Pitolisant

- Pitolisant prolongs the QT interval. The use of pitolisant should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval. Pitolisant should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval. The risk of QT prolongation may be greater in patients with hepatic or renal impairment due to higher concentrations of pitolisant. Patients with hepatic or renal impairment should be monitored for increased QTc.

○ Sodium oxybates/oxybate salts

- **Boxed warning** (sodium oxybate):
  - CNS depression
    - Xyrem is a CNS depressant, and respiratory depression can occur with sodium oxybate use.
  - Abuse and misuse
    - Sodium oxybate is the sodium salt of GHB. Abuse or misuse of illicit GHB is associated with CNS AEs, including seizure, respiratory depression, decreased consciousness, coma, and death.
- **Boxed warning** (oxybate salts)
  - CNS depression
    - Oxybate salts is a CNS depressant, and respiratory depression can occur with oxybate salts use.
  - Abuse and misuse
    - The active moiety of oxybate salts is GHB. Abuse or misuse of illicit GHB is associated with CNS AEs, including seizure, respiratory depression, decreased consciousness, coma, and death.
- *Respiratory Depression and Sleep-Disordered Breathing*
  - Sodium oxybate may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported.
  - During PSG, central sleep apnea and oxygen desaturation were observed in pediatric patients with narcolepsy treated with sodium oxybate.
  - Prescribers should be aware that increased central apneas and clinically relevant desaturation events have been observed with sodium oxybate administration in adult and pediatric patients.
- *Depression and suicidality*
  - In adult clinical trials in patients with narcolepsy (n = 781), there were 2 suicides and 2 attempted suicides in patients treated with sodium oxybate, including 3 patients with a previous history of depressive psychiatric disorder. Of the 2 suicides, 1 patient used sodium oxybate in conjunction with other drugs. Sodium oxybate was not involved in the second suicide. AEs of depression were reported by 7% of 781 patients treated with sodium oxybate, with 4 patients (< 1%) discontinuing because of depression. In most cases, no change in sodium oxybate treatment was required.
  - In a controlled adult trial, with patients randomized to fixed doses of 3 g, 6 g, or 9 g per night sodium oxybate or placebo, there was a single event of depression at the 3 g per night dose. In another adult controlled trial, with patients titrated from an initial 4.5 g per night starting dose, the incidences of depression were 1 (1.7%), 1 (1.5%), 2 (3.2%), and 2 (3.6%) for the placebo, 4.5 g, 6 g, and 9 g per night doses, respectively.
  - In the pediatric clinical trial in patients with narcolepsy (n = 104), 1 patient experienced suicidal ideation while taking sodium oxybate.
- *Other Behavioral or Psychiatric Adverse Reactions*
  - During adult clinical trials in patients with narcolepsy, 3% of 781 patients treated with sodium oxybate experienced confusion, with incidence generally increasing with dose.
  - Less than 1% of patients discontinued the drug because of confusion. Confusion was reported at all recommended doses from 6 g to 9 g per night. In a controlled trial in adults where patients were randomized to

fixed total daily doses of 3 g, 6 g, or 9 g per night or placebo, a dose-response relationship for confusion was demonstrated, with 17% of patients at 9 g per night experiencing confusion. In all cases in that controlled trial, the confusion resolved soon after termination of treatment. In Trial 3 where sodium oxybate was titrated from an initial 4.5 g per night dose, there was a single event of confusion in 1 patient at the 9 g per night dose. In the majority of cases in all adult clinical trials in patients with narcolepsy, confusion resolved either soon after termination of dosing or with continued treatment.
- Anxiety occurred in 5.8% of the 874 patients receiving sodium oxybate in adult clinical trials in another population.
- Other neuropsychiatric reactions reported in adult clinical trials in patients with narcolepsy and the post-marketing setting included hallucinations, paranoia, psychosis, aggression, and agitation.
- In the pediatric clinical trial in patients with narcolepsy, neuropsychiatric reactions, including acute psychosis, confusion, and anxiety, were reported while taking sodium oxybate.

▪ *Parasomnias*
- Sleepwalking, defined as confused behavior occurring at night and at times associated with wandering, was reported in 6% of 781 patients with narcolepsy treated with sodium oxybate in adult controlled and long-term OL studies, with < 1% of patients discontinuing due to sleepwalking. Rates of sleepwalking were similar for patients taking placebo and patients taking sodium oxybate in controlled trials. It is unclear if some or all of the reported sleepwalking episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Five instances of significant injury or potential injury were associated with sleepwalking during a clinical trial of sodium oxybate in patients with narcolepsy.

▪ *Use in patients sensitive to high sodium intake (sodium oxybate)*
- Sodium oxybate has a high salt content. In patients sensitive to salt intake (eg, those with HF, HTN, or renal impairment), the amount of daily sodium intake in each dose of sodium oxybate should be considered. Table 13 provides the approximate sodium content per sodium oxybate dose.

Table 13. Approximate sodium content per total nightly dose of sodium oxybate

Sodium oxybate dose/per night	Sodium content/total nightly exposure
3 g	550 mg
4.5 g	820 mg
6 g	1100 mg
7.5 g	1400 mg
9 g	1640 mg

○ Solriamfetol

▪ *Blood pressure and heart rate increases*:
- Solriamfetol increases systolic BP, diastolic BP, and heart rate in a dose-dependent fashion.
- Epidemiological data show that chronic elevations in BP increase the risk of major adverse CV events (MACE), including stroke, heart attack, and CV death. The magnitude of the increase in absolute risk is dependent on the increase in BP and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high BMI.
- BP should be assessed and controlled before initiation of treatment with solriamfetol. BP should be monitored regularly during treatment. New onset hypertension and exacerbations of pre-existing hypertension should be treated. Caution should be exercised when treating patients at higher risk of MACE, particularly patients with known CV and cerebrovascular disease, pre-existing hypertension, and patients with advanced age. Caution should be used with other drugs that increase BP and heart rate.
- The need for continued treatment should be periodically re-assessed. If a patient experiences increases in BP or heart rate that cannot be managed with dose reduction of solriamfetol or other appropriate medical intervention, drug discontinuation should be considered.
- Patients with moderate or severe renal impairment may be at higher risk of increases in BP and heart rate because of the prolonged half-life of solriamfetol.

▪ *Psychiatric symptoms*:
- Psychiatric AEs have been observed in clinical trials with solriamfetol, including anxiety, insomnia, and irritability.
- Solriamfetol has not been evaluated in patients with psychosis or bipolar disorders. Caution should be exercised when treating patients with solriamfetol who have a history of psychosis or bipolar disorders.
- Patients with moderate or severe renal impairment may be at a higher risk of psychiatric symptoms because of the prolonged half-life of solriamfetol.

- Patients treated with solriamfetol should be observed for the possible emergence or exacerbation of psychiatric symptoms. If psychiatric symptoms develop in association with the administration of solriamfetol, dose reduction or discontinuation of solriamfetol should be considered.

- **Adverse effects**
  - Armodafinil
    - The most common AEs (≥ 5%) vs placebo were headache (17 vs 9%), nausea (7 vs 3%), dizziness (5 vs 2%), and insomnia (5 vs 1%).
    - In PC clinical trials, 44 of the 645 patients (7%) who received armodafinil discontinued due to an AE compared to 16 of the 445 (4%) patients that received placebo. The most frequent reason for discontinuation was headache (1%).
  - Modafinil
    - The most common AEs (≥ 5%) vs placebo were headache (34 vs 23%), nausea (11 vs 3%), nervousness (7 vs 3%), rhinitis (7 vs 6%), diarrhea (6 vs 5%), back pain (6 vs 5%), anxiety (5 vs 1%), insomnia (5 vs 1%), dizziness (5 vs 4%), and dyspepsia (5 vs 4%).
    - In PC clinical trials, 74 of the 934 patients (8%) who received modafinil discontinued due to an AE compared to 3% of patients that received placebo. The most frequent reasons for discontinuation that occurred at a higher rate for modafinil than placebo patients were headache (2%), nausea, anxiety, dizziness, insomnia, chest pain, and nervousness (each < 1%).
  - Pitolisant
    - In the PC clinical trials conducted in patients with narcolepsy with or without cataplexy, the most common AEs (occurring in ≥ 5% of patients and at twice the rate of placebo) with the use of pitolisant were insomnia (6%), nausea (6%), and anxiety (5%).
  - Sodium oxybate
    - The most common AEs in adults (≥ 2% and more frequently than placebo) were nausea (8 to 20% vs 3%), dizziness (9 to 15% vs 4%), vomiting (2 to 11% vs 1%), somnolence (1 to 8% vs 4%), enuresis (3 to 7% vs 1%), and tremor (2 to 5% vs 0%).
    - The overall AE profile in the pediatric clinical trials was similar to that seen in the adult clinical trial program. The most common AEs of sodium oxybate in pediatric patients (≥ 5%) were enuresis (18%), nausea (17%), headache (16%), vomiting (16%), weight decreased (12%), decreased appetite (8%), and dizziness (6%).
    - Of the 398 patients with narcolepsy treated with sodium oxybate, 10.3% of patients discontinued because of AEs compared with 2.8% of patients receiving placebo. The most common AE leading to discontinuation was nausea (2.8%). The majority of AEs leading to discontinuation began during the first few weeks of treatment.
  - Oxybate salts
    - The most common AEs in the adult study (incidence ≥ 5% of oxybate salts-treated patients) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting.
    - AEs observed in clinical studies with sodium oxybate (≥ 2%), but not in the adult oxybate salts study, and which may be relevant for oxybate salts included pain, feeling drunk, pain in extremity, cataplexy, disturbance in attention, sleep paralysis, and disorientation.
  - Solriamfetol
    - The most common AEs (≥ 5% and greater than placebo) in either the narcolepsy or OSA populations vs placebo were headache (16 vs 7%), nausea (7 vs 4%), decreased appetite (9 vs 1%), insomnia (5 vs 4%), and anxiety (6 vs 1%).
    - In the 12-week PC clinical trials, 11 of the 396 patients (3%) who received solriamfetol discontinued because of an AE compared to 1 of the 226 patients (< 1%) who received placebo. The AEs resulting in discontinuation that occurred in more than 1 solriamfetol-treated patient and at a higher rate than placebo were: anxiety (2/396; < 1%), palpitations (2/396; < 1%), and restlessness (2/396; < 1%).
    - Drug abuse and dependence
      - Abuse
        - Solriamfetol has potential for abuse. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. The abuse potential of solriamfetol 300 mg, 600 mg, and 1200 mg (2, 3, and 4 times the maximum recommended dose, respectively) was assessed relative to phentermine, 45 mg and 90 mg, (a Schedule IV controlled substance) in a human abuse potential study in individuals (N = 43) experienced with the recreational use of stimulants. Results from this clinical study demonstrated that solriamfetol produced Drug Liking scores similar to or lower than phentermine. In this XO study, elevated mood was reported by 2.4% in the placebo group, 8 to 24% in the solriamfetol group, and 10 to 18% in the phentermine group. A “feeling of relaxation” was reported in 5% of the placebo group, 5 to 19% of the solriamfetol group, and 15 to 20% of the phentermine group (*Carter et al 2018, Solriamfetol prescribing information 2019*).

- Physicians should carefully evaluate patients for a recent history of drug abuse, especially those with a history of stimulant (eg, methylphenidate, amphetamine, or cocaine) or alcohol abuse, and follow such patients closely, observing them for signs of misuse or abuse of solriamfetol (eg, incrementation of doses, drug-seeking behavior).

- Dependence
  - In a long-term safety and maintenance of efficacy study, the effects of abrupt discontinuation of solriamfetol were evaluated following at least 6 months of solriamfetol use in patients with narcolepsy or OSA. The effects of abrupt discontinuation of solriamfetol were also evaluated during the 2-week safety follow-up periods in the Phase 3 studies. There was no evidence that abrupt discontinuation of solriamfetol resulted in a consistent pattern of AEs in individual patients that was suggestive of physical dependence or withdrawal.

- **Drug Interactions**
  - Modafinil/armodafinil
    - *Effects on CYP3A4/5 substrates*
      - The clearance of drugs that are substrates for CYP3A4/5 (eg, steroidal contraceptives, cyclosporine, midazolam, and triazolam) may be increased by modafinil/armodafinil via induction of metabolic enzymes, which results in lower systemic exposure. Dosage adjustment of these drugs should be considered when these drugs are used concomitantly with modafinil/armodafinil.
      - The effectiveness of steroidal contraceptives may be reduced when used with armodafinil/modafinil and for 1 month after discontinuation of therapy. Alternative or concomitant methods of contraception are recommended for patients taking steroidal contraceptives (eg, ethinyl estradiol) when treated concomitantly with modafinil/armodafinil and for 1 month after discontinuation of modafinil/armodafinil treatment.
      - Blood levels of cyclosporine may be reduced when used with modafinil/armodafinil. Monitoring of circulating cyclosporine concentrations and appropriate dosage adjustment for cyclosporine should be considered when used concomitantly with modafinil/armodafinil.
    - *Effects on CYP2C19 substrates*
      - Elimination of drugs that are substrates for CYP2C19 (eg, phenytoin, diazepam, propranolol, omeprazole, and clomipramine) may be prolonged by modafinil/armodafinil via inhibition of metabolic enzymes, with resultant higher systemic exposure. In individuals deficient in the CYP2D6 enzyme, the levels of CYP2D6 substrates which have ancillary routes of elimination through CYP2C19, such as TCAs and SSRIs, may be increased by co-administration of modafinil/armodafinil. Dose adjustments of these drugs and other drugs that are substrates for CYP2C19 may be necessary when used concomitantly with modafinil/armodafinil.
    - *Warfarin*
      - More frequent monitoring of prothrombin times/international normalized ratio (INR) should be considered whenever modafinil/armodafinil is co-administered with warfarin.
    - *MAOIs*
      - Caution should be used when concomitantly administering MAOIs and modafinil/armodafinil.
  - Pitolisant
    - Drugs having clinically important interactions with pitolisant:

Table 14. Clinically significant drug interactions with pitolisant

Effect of Other Drugs on pitolisant	
Strong CYP2D6 Inhibitors	
Clinical implication:	Concomitant administration of pitolisant with strong CYP2D6 inhibitors increases pitolisant exposure by 2.2-fold.
Prevention or management:	Reduce the dose of pitolisant by half.
Examples:	paroxetine, fluoxetine, bupropion
Strong CYP3A4 Inducers	
Clinical implication:	Concomitant use of pitolisant with strong CYP3A4 inducers decreases exposure of pitolisant by 50%.
Prevention or management:	Assess for loss of efficacy after initiation of a strong CYP3A4 inducer. For patients stable on pitolisant 8.9 mg or 17.8 mg once daily, increase the dose of pitolisant to reach double the original daily dose (ie, 17.8 mg or 35.6 mg, respectively) over 7 days. If concomitant dosing of a strong CYP3A4 inducer is discontinued, decrease pitolisant dosage by half.
Examples:	rifampin, carbamazepine, phenytoin
Histamine-1 (H_1) Receptor Antagonists	

Clinical implication:	Pitolisant increases the levels of histamine in the brain; therefore, H_1 receptor antagonists that cross the blood-brain barrier may reduce the effectiveness of pitolisant.
Prevention or management:	Avoid centrally acting H_1 receptor antagonists.
Examples:	pheniramine maleate, diphenhydramine, promethazine (antihistamines) imipramine, clomipramine, mirtazapine (tri or tetracyclic antidepressants)
QT interval prolongation	
Clinical implication:	Concomitant use of drugs that prolong the QT interval may add to the QT effects of pitolisant and increase the risk of cardiac arrhythmia.
Prevention or management:	Avoid the use of pitolisant in combination with other drugs known to prolong the QT interval.
Examples:	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide Class 3 antiarrhythmics: amiodarone, sotalol Antipsychotics: ziprasidone, chlorpromazine, thioridazine Antibiotics: moxifloxacin
Sensitive CYP3A4 Substrates	
Clinical implication:	Pitolisant is a borderline/weak inducer of CYP3A4. Therefore, reduced effectiveness of sensitive CYP3A4 substrates may occur when used concomitantly with pitolisant.
Prevention or management:	The effectiveness of hormonal contraceptives (eg, ethinyl estradiol) may be reduced when used with pitolisant and effectiveness may be reduced for 21 days after discontinuation of therapy.
Examples:	midazolam, hormonal contraceptives, cyclosporine

- Drugs having no clinically important interactions with pitolisant:
  - A clinical study was conducted to evaluate the concomitant use of pitolisant with modafinil or sodium oxybate. This study demonstrated no clinically relevant effect of modafinil or sodium oxybate on the PK of pitolisant and no effect of pitolisant on the PK of modafinil or sodium oxybate.
  - A clinical study showed that strong CYP3A4 inhibitors (eg, ketoconazole, grapefruit juice) have no effect on the PK of pitolisant.

- Sodium oxybate/oxybate salts
  - *Alcohol, sedative hypnotics, and CNS depressants*
    - Sodium oxybate/oxybate salts are contraindicated in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of sodium oxybate/oxybate salts.
  - *Divalproex sodium*
    - Concomitant use of sodium oxybate with divalproex sodium results in an increase in systemic exposure to GHB, which was shown to cause a greater impairment on some tests of attention and working memory in a clinical study. A similar increase in exposure is expected with concomitant use of oxybate salts and divalproex sodium; therefore, an initial dose reduction of oxybate salts is recommended when used concomitantly with divalproex sodium. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of oxybate salts and divalproex sodium is warranted.
- Solriamfetol
  - *MAOIs*
    - Solriamfetol should not be administered concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and noradrenergic drugs may increase the risk of a hypertensive reaction. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.
  - *Drugs that increase BP and/or heart rate*
    - Concomitant use of solriamfetol with other drugs that increase BP and/or heart rate has not been evaluated, and such combinations should be used with caution.
  - *Dopaminergic drugs*
    - Dopaminergic drugs that increase levels of dopamine or that bind directly to dopamine receptors might result in pharmacodynamic interactions with solriamfetol. Interactions with dopaminergic drugs have not been evaluated with solriamfetol. Caution should be used when concomitantly administering dopaminergic drugs with solriamfetol.

- **Risk Evaluation and Mitigation Strategy (REMS)**
  - Sodium oxybate/oxybate salts

- Sodium oxybate/oxybate salts are available only through a REMS program called the Xywav and Xyrem REMS program because of the risks of CNS depression and abuse and misuse.
- Notable requirements of the Xywav and Xyrem REMS program include:
  - Healthcare Providers who prescribe Xyrem and Xywav are specially certified.
  - Xywav and Xyrem will be dispensed only by the central pharmacy that is specially certified.
  - Xywav and Xyrem will be dispensed and shipped only to patients who are enrolled in the Xywav and Xyrem REMS Program with documentation of safe use.

DOSAGE AND ADMINISTRATION

- **Armodafinil**
  - Narcolepsy/OSA
    - The recommended dosage of armodafinil for patients with OSA or narcolepsy is 150 mg to 250 mg taken orally once a day as a single dose in the morning.
    - In patients with OSA, doses up to 250 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that these doses confer additional benefit beyond that of the 150 mg/day dose.
  - SWD
    - The recommended dosage of armodafinil for patients with SWD is 150 mg taken orally once a day as a single dose approximately 1 hour prior to the start of their work shift.
  - Hepatic impairment
    - The dosage of armodafinil should be reduced in patients with severe hepatic impairment.
- **Modafinil**
  - Narcolepsy/OSA
    - The recommended dosage of modafinil for patients with narcolepsy or OSA is 200 mg taken orally once a day as a single dose in the morning.
  - SWD
    - Doses up to 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg/day dose.
  - Hepatic impairment
    - In patients with severe hepatic impairment, the dose of modafinil should be reduced to one-half of that recommended for patients with normal hepatic function.
- **Pitolisant**
  - Recommended dosage
    - The recommended dosage of pitolisant is 17.8 to 35.6 mg administered orally once daily in the morning upon wakening. The dose should be titrated as follows:
      - Week 1: Initiate with a dosage of 8.9 mg (two 4.45 mg tablets) once daily
      - Week 2: Increase dosage to 17.8 mg (one 17.8 mg tablet) once daily
      - Week 3: May increase to the maximum recommended dosage of 35.6 mg (two 17.8 mg tablets) once daily
    - Dose may be adjusted based on tolerability.
    - If a dose is missed, patients should take the next dose the following day in the morning upon wakening.
    - It may take up to 8 weeks for some patients to achieve a clinical response.
  - Hepatic impairment
    - In patients with moderate hepatic impairment, pitolisant should be initiated at 8.9 mg once daily and increased after 14 days to a maximum dosage of 17.8 mg once daily.
    - Pitolisant is contraindicated in patients with severe hepatic impairment. Pitolisant has not been studied in patients with severe hepatic impairment.
  - Renal impairment and ESRD
    - In patients with moderate and severe renal impairment, pitolisant should be initiated at 8.9 mg once daily and increased after 7 days to a maximum dosage of 17.8 mg once daily.
    - Pitolisant is not recommended in patients with ESRD.
  - Concomitant use with strong CYP2D6 inhibitors and strong CYP3A4 inducers
    - Coadministration with strong CYP2D6 inhibitors
      - For patients receiving strong CYP2D6 inhibitors, pitolisant should be initiated at 8.9 mg once daily and increased after 7 days to a maximum dosage of 17.8 mg once daily.
      - For patients on a stable dose of pitolisant, the pitolisant dose should be reduced by half upon initiating strong CYP2D6 inhibitors.
    - Coadministration with strong CYP3A4 inducers
      - Concomitant use of pitolisant with strong CYP3A4 inducers decreases pitolisant exposure by 50%.
      - Patients should be assessed for loss of efficacy after initiation of a strong CYP3A4 inducer.

- For patients stable on pitolisant 8.9 mg or 17.8 mg once daily, the dose of pitolisant should be increased to double the original daily dose (ie, 17.8 mg or 35.6 mg, respectively) over 7 days.
- If concomitant dosing of a strong CYP3A4 inducer is discontinued, the pitolisant dosage should be decreased by half.

○ Patients who are known CYP2D6 poor metabolizers
- In patients known to be poor CYP2D6 metabolizers, pitolisant should be initiated at 8.9 mg once daily and titrated to a maximum dose of 17.8 mg once daily after 7 days.

• **Sodium oxybate/oxybate salts**

○ Adult dosing
- The recommended starting dose of sodium oxybate/oxybate salts is 4.5 g per night administered orally, divided into 2 doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later (see Table 15). The dosage should be increased by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dosage range of 6 g to 9 g per night orally. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

Table 15. Recommended adult sodium oxybate/oxybate salts dose regimen

If a patient's total nightly dose is:	Take at bedtime:	Take 2.5 to 4 hours later:
4.5 g	2.25 g	2.25 g
6 g	3 g	3 g
7.5 g	3.75 g	3.75 g
9 g	4.5 g	4.5 g

○ Pediatric dosing
- Sodium oxybate/oxybate salts are administered orally twice nightly. The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight, as specified in Table 16. The dosage may be gradually titrated based on efficacy and tolerability.

Table 16. Recommended pediatric sodium oxybate/oxybate salts dosage for patients ≥ 7 years of age*

Patient weight	Initial Dosage		Maximum Weekly Dosage Increase		Maximum Recommended Dosage	
	Take at bedtime:	Take 2.5 to 4 hours later:	Take at bedtime:	Take 2.5 to 4 hours later:	Take at bedtime:	Take 2.5 to 4 hours later:
< 20 kg†	There is insufficient information to provide specific dosing recommendations for patients who weigh < 20 kg.					
20 to < 30 kg	≤ 1 g	≤ 1 g	0.5 g	0.5 g	3 g	3 g
30 to < 45 kg	≤ 1.5 g	≤ 1.5 g	0.5 g	0.5 g	3.75 g	3.75 g
≥ 45 kg	≤ 2.25 g	≤ 2.25 g	0.75 g	0.75 g	4.5 g	4.5 g

*For patients who sleep > 8 hours per night, the first dose may be given at bedtime or after an initial period of sleep.
†In patients ≥ 7 years of age who weigh < 20 kg, a lower starting dosage, lower maximum weekly dosage increases, and lower total maximum nightly dosage should be considered.
Note: Unequal dosages may be required for some patients to achieve optimal treatment.

○ Important administration instructions
- The first dose of sodium oxybate/oxybate salts should be taken at least 2 hours after eating.
- Both doses should be prepared prior to bedtime. Prior to ingestion, each dose should be diluted with approximately one-fourth cup (approximately 60 mL) of water in the empty pharmacy containers provided. Patients should take both doses while in bed and lie down immediately after dosing as oxybate/oxybate salts may cause them to fall asleep abruptly without first feeling drowsy. Patients will often fall asleep within 5 minutes of taking oxybate/oxybate salts, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night. Patients should remain in bed following ingestion of the first and second doses, and should not take the second dose until 2.5 to 4 hours after the first dose. Patients may need to set an alarm to awaken for the second dose. Rarely, patients may take up to 2 hours to fall asleep.
- If the second dose is missed, that dose should be skipped and the drug should not be taken again until the next night. Both doses should never be taken at one time.

○ Patients transitioning from sodium oxybate to oxybate salts
- On the first night of dosing with oxybate salts, treatment should be initiated at the same dose (g for g) and regimen as sodium oxybate. The dose should be titrated as needed based on efficacy and tolerability.

○ Hepatic impairment

- The recommended starting dosage of sodium oxybate/oxybate salts in patients with hepatic impairment is one-half of the original dosage per night administered orally, divided into 2 doses.

○ Dose adjustment with co-administration of divalproex sodium
- When initiating divalproex sodium in patients receiving a stable dosage of sodium oxybate/oxybate salts, a reduction of the sodium oxybate/oxybate salts dosage by at least 20% is recommended with initial concomitant use. When initiating sodium oxybate/oxybate salts in patients already taking divalproex sodium, a lower starting dosage of sodium oxybate/oxybate salts is recommended. Subsequently, the dosage can be adjusted based on individual clinical response and tolerability.

• **Solriamfetol**
○ Solriamfetol should be administered upon awakening with or without food. Patients should avoid taking solriamfetol within 9 hours of planned bedtime because of the potential to interfere with sleep if taken too late in the day.
○ Solriamfetol 75 mg tablets are functionally scored tablets that can be split in half (37.5 mg) at the score line.
○ Narcolepsy
- Solriamfetol should be initiated at 75 mg once daily in adults with narcolepsy. The recommended dose range is 75 to 150 mg once daily. Based on efficacy and tolerability, the dosage of solriamfetol may be doubled at intervals of at least 3 days. The maximum recommended dose is 150 mg once daily. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related AEs.

○ OSA
- Solriamfetol should be initiated at 37.5 mg once daily in adults with OSA. The recommended dosage range is 37.5 to 150 mg once daily. Based on efficacy and tolerability, the dosage of solriamfetol may be doubled at intervals of at least 3 days. The maximum recommended dosage is 150 mg once daily. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related AEs.

○ Renal impairment
- Moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 59 mL/min/1.73 m^2): dosing should be initiated at 37.5 mg once daily. Based on efficacy and tolerability, the dose may be increased to a maximum of 75 mg once daily after at least 7 days.
- Severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2): a dose of 37.5 mg should be administered daily. The maximum recommended dose is 37.5 mg.
- ESRD (eGFR < 15 mL/min/1.73 m^2): solriamfetol is not recommended for use in patients with ESRD.

SPECIFIC POPULATIONS

• **Geriatrics**
○ Armodafinil
- In elderly patients, elimination of armodafinil and its metabolites may be reduced as a consequence of aging. Therefore, consideration should be given to the use of lower doses and close monitoring in this population.

○ Modafinil
- In clinical trials, experience in a limited number of modafinil-treated patients who were > 65 years of age showed an incidence of AEs similar to other age groups. In elderly patients, elimination of modafinil and its metabolites may be reduced as a consequence of aging. Therefore, consideration should be given to the use of lower doses and close monitoring in this population.

○ Pitolisant
- Limited PK data are available in healthy elderly patients. A PK study that compared 12 elderly patients (68 to 82 years of age) to 12 healthy adults (18 to 45 years of age) did not reveal any significant differences in drug exposure.
- Of the total number of patients with narcolepsy in clinical studies of pitolisant, 14 patients (5%) were ≥ 65 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients in these clinical trials, but greater sensitivity of some older individuals cannot be ruled out.

○ Sodium oxybate/oxybate salts
- Clinical studies of sodium oxybate/oxybate salts in patients with narcolepsy did not include sufficient numbers of patients ≥ 65 years of age to determine whether they respond differently from younger patients. In controlled trials of sodium oxybate in another population, 39 (5%) of 874 patients were ≥ 65 years of age. Discontinuations of treatment due to AEs were increased in the elderly compared to younger adults (20.5% vs 18.9%). Frequency of headaches was markedly increased in the elderly (39% vs 19%). The most common AEs were similar in both age categories.

○ Solriamfetol
- Of the total number of patients in the narcolepsy and OSA clinical studies treated with solriamfetol, 13% (123/930) were 65 years of age or over.
- No clinically meaningful differences in safety or efficacy were observed between elderly and younger patients.

- Solriamfetol is predominantly eliminated by the kidney. Because elderly patients are more likely to have decreased renal function, dosing may need to be adjusted based on eGFR in these patients. Consideration should be given to the use of lower doses and close monitoring in this population.

- **Pediatrics**
  - Armodafinil
    - Safety and efficacy in pediatric patients have not been established.
  - Modafinil
    - Safety and efficacy in pediatric patients have not been established.
  - Pitolisant
    - The safety and effectiveness of pitolisant in pediatric patients have not been established.
    - Limited PK data from 24 pediatric patients with narcolepsy (7 to < 18 years of age) receiving a single dose of pitolisant suggested that pediatric patients have higher exposure to pitolisant than adults. The exposure (C_{max} and AUC) of pitolisant was 2-fold higher in pediatric patients 12 to < 18 years and 3-fold higher in pediatric patients 7 to < 12 years compared to adults.
  - Sodium oxybate/oxybate salts
    - The safety and effectiveness of sodium oxybate in the treatment of cataplexy or EDS in pediatric patients ≥ 7 years of age with narcolepsy have been established in a DB, PC, RW study.
    - The safety and effectiveness of oxybate salts for the treatment of cataplexy or EDS in pediatric patients ≥ 7 years of age with narcolepsy have been established. Oxybate salts has not been studied in a pediatric clinical trial. Use of oxybate salts in pediatric patients ≥ 7 years of age with narcolepsy is supported by evidence from the RW study of sodium oxybate, a study in adults showing a treatment effect of oxybate salts similar to that observed with sodium oxybate, PK data of sodium oxybate from adult and pediatric patients, and PK data of oxybate salts from healthy adult volunteers.
    - Safety and effectiveness of sodium oxybate and oxybate salts in pediatric patients < 7 years of age have not been established.
  - Solriamfetol
    - Safety and efficacy in pediatric patients have not been established. Clinical studies of solriamfetol in pediatric patients have not been conducted.
- **Renal dysfunction**
  - Pitolisant
    - The PK of pitolisant in patients with ESRD (eGFR of < 15 mL/minute/1.73 m^2) is unknown.
    - See dosing section above.
  - Solriamfetol
    - See dosing section above.
- **Hepatic dysfunction**
  - Armodafinil
    - See dosing section above.
  - Modafinil
    - See dosing section above.
  - Pitolisant
    - Pitolisant is contraindicated in patients with severe hepatic impairment (Child Pugh C) as it has not been studied in this population. Pitolisant is extensively metabolized by the liver and there is a significant increase in pitolisant exposure in patients with moderate hepatic impairment.
    - See dosing section above for patients with moderate hepatic impairment.
    - Patients with mild hepatic impairment (Child Pugh A) should be monitored. No dosage adjustment of pitolisant is recommended in patients with mild hepatic impairment.
  - Sodium oxybate/oxybate salts
    - See dosing section above.
- **Pregnancy and nursing**
  - Armodafinil
    - There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to armodafinil during pregnancy. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-866-404-4106.
    - Limited available data on armodafinil use in pregnant women are insufficient to inform a drug associated risk of adverse pregnancy outcomes.
    - There are no data on the presence of armodafinil or its metabolites in human milk, the effects on the breastfed infant, or the effect of this drug on milk production. Modafinil was present in rat milk when animals were dosed during the lactation period. The developmental and health benefits of breastfeeding should be considered along

with the mother's clinical need for armodafinil and any potential AEs on the breastfed child from armodafinil or from the underlying maternal condition.

- Modafinil
  - A pregnancy registry has been established to collect information on the pregnancy outcomes of women exposed to modafinil. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-866-404-4106.
  - There are no adequate and well-controlled studies of modafinil in pregnant women.
  - It is not known whether modafinil or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when modafinil is administered to a nursing woman.
  - A pregnancy registry reported an elevated rate of major congenital anomalies (17%) and cardiac anomalies (4%) among women in the U.S. exposed to modafinil and/or armodafinil (some took additional drugs). Based on these data, Health Canada issued a warning that modafinil is contraindicated in women who are pregnant or may become pregnant in June 2019 (*Eichler et al 2019*).
- Pitolisant
  - There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to pitolisant during pregnancy. Patients should be encouraged to enroll in the pitolisant pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call 1-800-833-7460.
  - Available case reports from clinical trials and postmarketing reports with pitolisant use in pregnant women have not determined a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.
  - There are no data on the presence of pitolisant in human milk, the effects on the breastfed infant, or the effect of this drug on milk production.
  - Pitolisant is present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for pitolisant and any potential AEs on the breastfed child from pitolisant or from the underlying maternal condition.
- Sodium oxybate/oxybate salts
  - There are no adequate data on the developmental risk associated with the use of sodium oxybate or oxybate salts in pregnant women.
  - GHB is excreted in human milk after oral administration of sodium oxybate. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sodium oxybate/oxybate salts and any potential AEs on the breastfed infant from sodium oxybate or from the underlying maternal condition.
- Solriamfetol
  - Pregnancy Exposure Registry There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to solriamfetol during pregnancy. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-877-283-6220 or contacting the company at *www.SunosiPregnancyRegistry.com*.
  - Available data from case reports are not sufficient to determine drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes.
  - There are no data available on the presence of solriamfetol or its metabolites in human milk, the effects on the breastfed infant, or the effect of this drug on milk production.
  - Solriamfetol is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for solriamfetol and any potential AEs on the breastfed child from solriamfetol or from the underlying maternal condition.

APPENDICES

Appendix A. Definitions of terms (*Freedman 2019*)

- Epoch: An epoch is a standard 30-second interval of a PSG to which a sleep stage is assigned. In special situations, an epoch can be longer or shorter.
- Sleep onset: The recommended definition for sleep onset for the MWT is 3 consecutive epochs of stage 1 sleep or 1 epoch of any other stage of sleep.
- Sleep latency: Sleep latency is the duration from lights out to the onset of sleep.
- Mean sleep latency: The mean sleep latency is the average of the sleep latencies determined during a test.

Appendix B. Multiple Sleep Latency Test (MSLT) (*American Sleep Association Web site, Thorpy 1992*)

- The MSLT is a diagnostic tool that measures the time it takes an individual to fall asleep in ideal quiet conditions during the day. It objectively measures daytime sleepiness. Colloquially known as the daytime nap study, the MSLT is also a standard tool used to diagnose idiopathic hypersomnia and narcolepsy.
- The MSLT is based on the fact that the more tired an individual is, the faster they will fall asleep. In addition to assessing for narcolepsy and idiopathic hypersomnia, the MSLT is used to evaluate insomnia, OSA, circadian rhythm sleep disorders, and response to treatment following effective therapy for disorders that cause sleepiness.
- For correct interpretation, the MSLT must be performed following an all-night PSG.
- The MSLT consists of 5 nap opportunities to determine both severity of sleepiness and presence of 2 or more sleep onset REM periods for the diagnosis of narcolepsy. A shorter 4-nap test may be performed for determination of excessive sleepiness, but this test is not reliable for the diagnosis of narcolepsy unless at least 2 sleep onset REM periods (SOREMPs) have occurred.
- The absence of sleep on any nap opportunity is recorded as a sleep latency of 20 minutes.
- Mean sleep latency times (min) are interpreted as follows:
  - 0 to 5: severe sleepiness
  - 5 to 10: moderate sleepiness
  - 10 to 15: mild sleepiness

Appendix C. Maintenance of Wakefulness Test (MWT) (*Freedman 2019*)

- The MWT objectively measures the ability of an individual to remain awake for a defined period of time. It is based on the premise that individuals with a greater degree of sleepiness are less likely to remain awake than individuals with less sleepiness.
- The MWT is primarily used in a research setting to assess an intervention's ability to improve alertness. Some commercial driving companies utilize the MWT to assess a driver's ability to operate a vehicle safely, although the utility of the MWT in clinical practice is limited by the test's inability to accurately predict safety in real world settings.
- MWT Protocol:
  - The MWT should be performed following a standard protocol. Using a protocol minimizes the variables that can impact sleep latency, the test's primary measure. Several acceptable protocols exist including the following, which was endorsed by a task force from the AASM:
    - Patients should maintain their normal routine prior to the test. Upon arrival, they should be questioned to determine whether their sleep prior to the test was adequate in quality and quantity, and whether they feel alert. The MWT should be delayed if the patient reports suboptimal sleep or not feeling alert. A PSG on the prior night is not necessary. Urine drug testing may be indicated to ensure that the result is not influenced by substances other than prescribed medications and is usually performed on the morning of the MWT or as directed by the sleep clinician.
    - The MWT begins 1.5 to 3 hours after the patient's usual wake-up time. The patient is placed in a room with little or no external light. The only light source should be dim, slightly behind the patient's head, and just out of the patient's field of vision. The room temperature is based on the patient's comfort level. The patient sits upright in bed, with their back and head supported, and is instructed to try to stay awake as long as possible. Monitoring includes electroencephalography (EEG), electrooculography, mental or submental electromyography, and electrocardiography.
    - A session is ended after unequivocal sleep, or after 40 minutes if sleep does not occur. Sleep is considered unequivocal after 3 consecutive epochs of stage 1 sleep or 1 epoch of any other stage of sleep. For each session, the sleep latency is recorded. It is documented as being 40 minutes if the patient does not fall asleep.
    - This is repeated every 2 hours, until the patient has completed 4 sessions.
- Interpretation of MWT:
  - The primary measure from the MWT is the mean sleep latency. There are few data regarding what constitutes a normal mean sleep latency, as measured by the MWT. Among healthy individuals who complete the 4 session, 40-minute protocol described above, the mean sleep latency is approximately 30 minutes, with > 97% of individuals having a mean sleep latency ≥ 8 minutes. As a result, a mean sleep latency < 8 minutes is generally considered abnormal. Staying awake for at least 40 minutes during all 4 sessions is strong objective evidence that an individual can stay awake. A mean sleep latency between 8 and 40 minutes has uncertain significance.

Appendix D. Epworth Sleepiness Scale (ESS) (*Johns 1991*)

- The ESS is a self-administered questionnaire that provides a measurement of an individual's general level of daytime sleepiness.
- Patients are asked to rate on a scale of 0 to 3 how likely they would be to doze off or fall asleep in 8 situations that involve low levels of stimulation, relative immobility, and relaxation based on their usual way of life in recent times. The following question is rated for each situation using a scale of 0 to 3 as defined below:

- How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:
  - 0 = would never doze
  - 1 = slight chance of dozing
  - 2 = moderate chance of dozing
  - 3 = high chance of dozing
- The 8 situations include:
  - Sitting and reading
  - Watching TV
  - Sitting, inactive in a public place (eg, a theater or a meeting)
  - As a passenger in a car for an hour without a break
  - Lying down to rest in the afternoon when circumstances permit
  - Sitting and talking to someone
  - Sitting quietly after a lunch without alcohol
  - *In a car, while stopped for a few minutes in the traffic*
- Interpretation of ESS scoring (range, 1 to 24):
  - 1 to 6 points: normal sleep
  - 7 to 8 points: average sleepiness
  - 9 to 24 points: abnormal (possibly pathologic) sleepiness

Appendix E. Karolinska Sleepiness Scale (KSS) (*Akerstedt & Gillberg 1990*)

- The KSS is a 9-point Likert scale often used when conducting studies involving self-reported, subjective assessment of an individual's level of drowsiness at the time. The KSS scores are defined as follows:
  - 1 = extremely alert
  - 3 = alert
  - 5 = neither alert nor sleepy
  - 7 = sleepy, no difficulty remaining awake
  - 9 = extremely sleepy, fighting sleep
    - The steps in between have a scale value but no verbal label.

Appendix F. Stanford Sleepiness Scale (SSS) (*upenn.edu Web site*)

- The SSS is a subjective measure of sleepiness, frequently used for both research and clinical purposes. Whereas an instrument like the ESS examines general experiences of sleepiness over the course of an entire day, the SSS evaluates sleepiness at specific moments in time. Consisting of only 1 item, the scale requires respondents to select 1 of 7 statements best representing their level of perceived sleepiness. As a single-item measure, the scale is best suited for repeated use over the course of a research study or treatment intervention. The rating scale is as follows:
  - 1 = feeling active, vital, alert, or wide awake
  - 2 = functioning at high levels, but not at peak; able to concentrate
  - 3 = awake, but relaxed; responsive but not fully alert
  - 4 = somewhat foggy, let down
  - 5 = sleepy, woozy, fighting sleep; prefer to lie down
  - 6 = no longer fighting sleep, sleep onset soon; having dream-like thoughts
  - 7 = asleep

Appendix G. Sustained Attention to Response Task (SART) (*Fronczek et al 2006*)

- A number from 1 to 9 is shown to the patient 225 times in white on a black computer screen over a 4.3-minute period in a quiet room with dimmed lights. Each of the 9 numbers is shown 25 times in random order. The font size is chosen at random from 26, 28, 36, or 72 points. The numbers are presented in a predetermined and quasirandom way so that identical numbers were not clustered. Each number is presented for 250 milliseconds, followed by a blank screen for 900 milliseconds. Patients have to respond to the appearance of each number by pressing a small button, except when the number is a 3. Patients have to press the button before the next number appears and are instructed that accuracy is more important than speed. A complete SART takes 4 minutes and 20 seconds to perform. The SART error score consists of the total number of errors, expressed as the sum of the times a key was pressed when a 3 was presented, and the times when no key was pressed when it should have been.

Appendix H. AASM grading of evidence (*Morgenthaler et al 2007a*)

Classification of evidence

Evidence levels	Study design

I	Randomized, well-designed trials with low alpha and beta error,* or meta-analyses of RCTs with homogeneity of results
II	Randomized trials with high alpha and beta error, methodologic problems, or high-quality cohort studies*
III	Nonrandomized concurrently controlled studies (case-control studies)
IV	Case-control or cohort studies with methodological problems, or case series
V	Expert opinion, or studies based on physiology or bench research

*Alpha (type I error) refers to the probability that the null hypothesis is rejected when in fact it is true (generally acceptable at 5% or less, or $p < 0.05$). Beta (Type II error) refers to the probability that the null hypothesis is mistakenly accepted when in fact it is false (generally, trials accept a beta error of 0.20). The estimation of Type II error is generally the result of a power analysis. The power analysis takes into account the variability and the effect size to determine if sample size is adequate to find a difference in means when it is present (power generally acceptable at 80 to 90%).

Levels of recommendation

Term	Definition
Standard	This is a generally accepted patient-care strategy that reflects a high degree of clinical certainty. The term standard generally implies the use of level 1 evidence, which directly addresses the clinical issue, or overwhelming level 2 evidence.
Guideline	This is a patient-care strategy that reflects a moderate degree of clinical certainty. The term guideline implies the use of level 2 evidence or a consensus of level 3 evidence.
Option	This is a patient-care strategy that reflects uncertain clinical use. The term option implies either inconclusive or conflicting evidence or conflicting expert opinion.

Appendix I. EAN grading of evidence (*Brainin et al 2004*)

Evidence classification scheme for a therapeutic intervention

Evidence levels	Definition
Class I	An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required: (a) randomization concealment (b) primary outcome(s) is/are clearly defined (c) exclusion/inclusion criteria are clearly defined (d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias (e) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
Class II	Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a through e above or an RCT in a representative population that lacks 1 criteria (a) through (e)
Class III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment
Class IV	Evidence from uncontrolled studies, case series, case reports, or expert opinion

Evidence classification scheme for a diagnostic measure

Evidence levels	Definition
Level A	Established as effective, ineffective, or harmful) requires at least 1 convincing class I study or at least 2 consistent, convincing class II studies
Level B	Probably effective, ineffective, or harmful) requires at least 1 convincing class II study or overwhelming class III evidence
Level C	Possibly effective, ineffective, or harmful) rating requires at least 2 convincing class III studies

Appendix J. Micromedex recommendation, efficacy, and evidence ratings (*Micromedex Web site 2019*)

Strength of recommendation

Class I	Recommended	The given test or treatment has been proven to be useful, and should be performed or administered
Class IIa	Recommended in most cases	The given test, or treatment is generally considered to be useful, and is indicated in most cases.
Class IIb	Recommended in some cases	The given test, or treatment may be useful, and is indicated in some, but not most, cases.
Class III	Not recommended	The given test, or treatment is not useful, and should be avoided.
Class indeterminate	Evidence inconclusive	

Strength of evidence	
Category A	Category A evidence is based on data derived from: Meta-analyses of RCTs with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.
Category B	Category B evidence is based on data derived from: Meta-analyses of RCTs with conflicting conclusions with regard to the directions and degrees of results between individual studies. RCTs that involved small numbers of patients or had significant methodological flaws (eg, bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (eg, cohort studies, case-control studies, observational studies).
Category C	Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series.
No evidence	

Efficacy		
Class I	Effective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective.
Class IIa	Evidence favors efficacy	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
Class IIb	Evidence is inconclusive	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
Class III	Ineffective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective.

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Publication date: 12/2/2020

Prior Authorization Guideline

Guideline Name Viekira (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets)

1 . Indications

Drug Name: Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets)
Chronic Hepatitis C Indicated for the treatment of adult patients with chronic hepatitis C virus (HCV): a) genotype 1b without cirrhosis or with compensated cirrhosis, and b) genotype 1a without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.

2 . Criteria

Product Name: Viekira Pak	
Diagnosis	Chronic Hepatitis C - Genotype 1a or Mixed Genotype 1 Infection – without Cirrhosis AND without Liver Transplant
Approval Length	12 Week(s)
Guideline Type	Prior Authorization
Approval Criteria **1** - Submission of medical records (e.g., chart notes, laboratory values) documenting diagnosis of chronic hepatitis C genotype 1a or mixed genotype 1 infection	

AND

2 - Patient is without cirrhosis

AND

3 - Used in combination with ribavirin

AND

4 - Patient is without decompensated liver disease (e.g., Child-Pugh Class B or C)

AND

5 - Prescribed by or in consultation with one of the following:

- Hepatologist
- Gastroenterologist
- Infectious disease specialist
- HIV specialist certified through the American Academy of HIV Medicine

AND

6 - Patient has not experienced failure with a previous treatment regimen that includes a HCV NS3/4A protease inhibitor [e.g., Incivek (telaprevir), Olysio (simeprevir), Victrelis (boceprevir)] or an NS5A inhibitor (Daklinza [daclatasvir])

AND

7 - Patient is not receiving Viekira in combination with another HCV direct acting antiviral agent [e.g., Harvoni (ledipasvir/sofosbuvir), Sovaldi (sofosbuvir)]

Product Name: Viekira Pak	
Diagnosis	Chronic Hepatitis C - Genotype 1a or Mixed Genotype 1 Infection – with Cirrhosis AND without Liver Transplant
Approval Length	24 Week(s)
Guideline Type	Prior Authorization
Approval Criteria	

1 - Submission of medical records (e.g., chart notes, laboratory values) documenting diagnosis of chronic hepatitis C genotype 1a or mixed genotype 1 infection

AND

2 - Submission of medical records (e.g., chart notes, laboratory values) documenting that the patient has cirrhosis

AND

3 - Used in combination with ribavirin

AND

4 - Patient is without decompensated liver disease (e.g., Child-Pugh Class B or C)

AND

5 - Prescribed by or in consultation with one of the following:

- Hepatologist
- Gastroenterologist
- Infectious Disease Specialist
- HIV Specialist Certified through the Academy of HIV Medicine

AND

6 - Patient has not experienced failure with a previous treatment regimen that includes a HCV NS3/4A protease inhibitor [e.g., Incivek (telaprevir), Olysio (simeprevir), Victrelis (boceprevir)] or an NS5A inhibitor (Daklinza [daclatasvir])

AND

7 - Patient is not receiving Viekira in combination with another HCV direct acting antiviral agent [e.g., Harvoni (ledipasvir/sofosbuvir), Sovaldi (sofosbuvir)]

Product Name: Viekira Pak	
Diagnosis	Chronic Hepatitis C - Genotype 1b - without Liver Transplant
Approval Length	12 Week(s)

Guideline Type	Prior Authorization

Approval Criteria

1 - Submission of medical records (e.g., chart notes, laboratory values) documenting diagnosis of chronic hepatitis C genotype 1b

AND

2 - Patient is without decompensated liver disease (e.g., Child-Pugh Class B or C)

AND

3 - Prescribed by or in consultation with one of the following:

- Hepatologist
- Gastroenterologist
- Infectious Disease Specialist
- HIV Specialist Certified through the Academy of HIV Medicine

AND

4 - Patient has not experienced failure with a previous treatment regimen that includes a HCV NS3/4A protease inhibitor [e.g., Incivek (telaprevir), Olysio (simeprevir), Victrelis (boceprevir)] or an NS5A inhibitor (Daklinza [daclatasvir])

AND

5 - Patient is not receiving Viekira in combination with another HCV direct acting antiviral agent [e.g., Harvoni (ledipasvir/sofosbuvir), Sovaldi (sofosbuvir)]

Product Name: Viekira Pak	
Diagnosis	Chronic hepatitis C - Genotype 1 (Regardless of Subgenotype) – Liver Transplant Recipient
Approval Length	24 Week(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Submission of medical records (e.g., chart notes, laboratory values) documenting diagnosis of chronic hepatitis C genotype 1

AND

2 - Documentation that the patient is a liver transplant recipient

AND

3 - Submission of medical records (e.g., chart notes or laboratory values) documenting normal hepatic function and mild fibrosis (e.g., METAVIR fibrosis score less than or equal to F2)

AND

4 - Used in combination with ribavirin

AND

5 - Prescribed by or in consultation with one of the following:

- Hepatologist
- Gastroenterologist
- Infectious disease specialist
- HIV specialist certified through the American Academy of HIV Medicine

AND

6 - Patient has not experienced failure with a previous treatment regimen that includes a HCV NS3/4A protease inhibitor [e.g., Incivek (telaprevir), Olysio (simeprevir), Victrelis (boceprevir)] or an NS5A inhibitor (Daklinza [daclatasvir])

AND

7 - Patient is not receiving Viekira in combination with another HCV direct acting antiviral agent [e.g., Harvoni (ledipasvir/sofosbuvir), Sovaldi (sofosbuvir)]

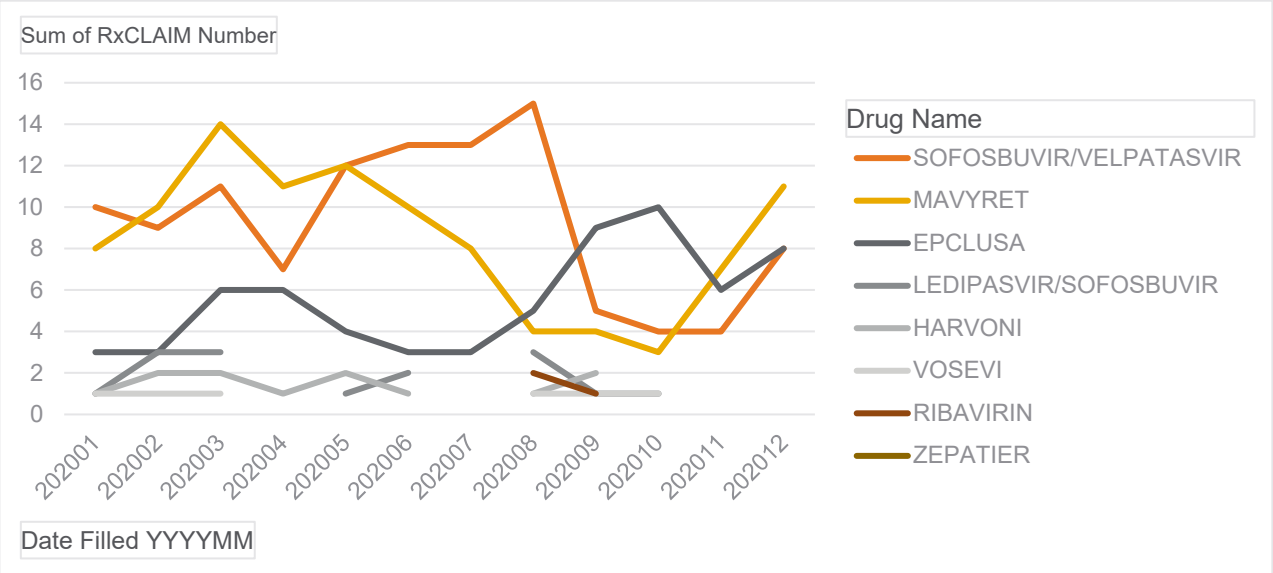
Nevada Medicaid

Hepatitis C Treatment

Fee for Service

January 1, 2020 – December 31, 2020

Drug Name	Members	Count of Claims	Total Days Supply	Total Quantity
EPCLUSA	27	66	1,932	1,932
HARVONI	5	12	336	336
LEDIPASVIR/SOFOSBUVIR	5	15	420	420
MAVYRET	55	102	2,912	8,736
RIBAVIRIN	2	4	94	564
SOFOSBUVIR/VELPATASVII	47	111	3,220	3,220
VOSEVI	2	6	168	168
ZEPATIER	1	1	28	28



HH. Anti-Hepatitis Agents

Therapeutic Class: Anti-Hepatitis Agents
Last Reviewed by the DUR Board: July 26, 2018

Anti-Hepatitis Agents are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Approval will be given if the following criteria are met and documented:

a. Daklinza® (daclatasvir) for genotype 1 or 3

1. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 or genotype 3 (submission of medical records e.g., chart notes, laboratory values); and

2. The medication is used in combination with Sovaldi® (sofosbuvir); and

3. One of the following:

a. The recipient is without decompensated cirrhosis and is not a liver transplant recipient; or

b. Both of the following:

1. The recipient has decompensated cirrhosis and/or is a liver transplant recipient; and

2. The medication is used in combination with Ribavirin.

4. The recipient has not failed a prior HCV NS5A-containing regimen (e.g., Daklinza); and

5. The medication must be prescribed by or in consultation with one of the following:

a. Hepatologist

b. Gastroenterologist

c. Infectious Disease Specialist

d. HIV Specialist (certified through the American Academy of HIV Medicine)

6. Prior authorization approval will be for 12 weeks.

b. Epclusa® (sofosbuvir and velpatasvir)

1. The following are required for all Epclusa® treatment:

a. The recipient is not receiving Epclusa® (sofosbuvir and velpatasvir) in combination with another HCV direct acting antiviral agent (e.g., Sovaldi®, Olysio®); and

b. The medication must be prescribed by or in consultation with one of the following:

1. Hepatologist

2. Gastroenterologist

3. Infectious Disease Specialist

4. HIV Specialist (certified through the American Academy of HIV Medicine)

2. Genotype 1, 2, 3, 4, 5 or 6, without decompensated liver disease

a. The recipient has a documented diagnosis of chronic hepatitis C virus genotype 1, 2, 3, 4, 5 or 6 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient must not have decompensated liver disease; and

c. Epclusa® must be used alone; and

d. The request is FDA approved for recipient weight and age; and

e. Prior authorization approval will be for 12 weeks.

3. Genotype 1, 2, 3, 4, 5 or 6 with decompensated liver disease

a. The recipient has a documented diagnosis of chronic hepatitis C virus genotype 1, 2, 3, 4, 5 or 6 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient has decompensated liver disease; and

c. Epclusa® is being used in combination with Ribavirin; and

d. The request is FDA approved for recipient weight and age; and

e. Prior authorization approval will be for 24 weeks.

4. Genotype 1, 2, 3, 4, 5 or 6 Ribavirin intolerance/ineligible or prior Sovaldi® (sofosbuvir) or NS5A-based treatment failure.

   a. The recipient has a documented diagnosis of chronic hepatitis C virus genotype 1, 2, 3, 4, 5 or 6 (submission of medical records e.g., chart notes, laboratory values); and

   b. The recipient has decompensated liver disease; and

      1. One of the following:

         a. The recipient is Ribavirin intolerant or ineligible; or

         b. Both of the following:

            1. The recipient has had prior failure (defined as viral relapse, breakthrough while on therapy, or is a non-responder to therapy) to Sovaldi® or NS5A-based treatment; and

            2. Epclusa® is used in combination with Ribavirin®.

   c. Prior authorization approval will be for 24 weeks.

c. Harvoni® (ledipasvir/sofosbuvir)

   1. The following are required for all Harvoni® treatment:

      a. The recipient is not receiving Harvoni® in combination with another HCV direct acting antiviral agent (e.g., Sovaldi®, Olysio®); and

      b. The medication must be prescribed by or in consultation with one of the following:

         1. Hepatologist

         2. Gastroenterologist

         3. Infectious Disease Specialist

         4. HIV Specialist (certified through the American Academy of HIV Medicine)

   2. Genotype 1, treatment naïve, without cirrhosis and pre-treatment HCV RNA is less than six million IU/mL

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient does not have cirrhosis; and

c. The recipient is treatment naïve; and

d. Medical records documenting pre-treatment HCV RNA less than six million IU/mL must be submitted; and

e. Prior authorization approval will be for eight weeks.

3. Genotype 1, treatment naïve, without cirrhosis and pre-treatment HCV RNA is greater than or equal to six million IU/mL

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient does not have cirrhosis; and

c. The recipient is treatment naïve; and

d. Medical records documenting pre-treatment HCV RNA greater than or equal to six million IU/mL must be submitted; and

e. Prior authorization approval will be for 12 weeks.

4. Genotype 1, treatment naïve with compensated cirrhosis

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

b. Submission of medical records (e.g., chart notes, laboratory values) documenting that the recipient has cirrhosis; and

c. The recipient is treatment naïve; and

d. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

e. Prior authorization approval will be for 12 weeks.

5. Genotype 1, treatment experienced without cirrhosis

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient does not have cirrhosis; and

c. One of the following:

1. The recipient has experienced treatment failure with a previous treatment regimen that included peginterferon plus Ribavirin or an HCV protease inhibitor (e.g., Incivek® (telaprevir), Olysio® (simeprevir), Victrelis® (boceprevir)) plus peginterferon plus Ribavirin; or

2. Both of the following:

a. The recipient has experienced treatment failure with a previous treatment regimen that included Sovaldi® (sofosbuvir) except in combination with Olysio® (simeprevir); and

b. The medication is used in combination with Ribavirin.

d. Prior authorization approval will be for 12 weeks.

6. Genotype 1, Ribavirin eligible, treatment experienced and with compensated cirrhosis

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

b. Submission of medical records (e.g., chart notes, laboratory values) documenting that the recipient has cirrhosis; and

c. The recipient has experienced treatment failure with a previous treatment regimen that included peginterferon plus Ribavirin or an HCV protease inhibitor (e.g., Incivek® (telaprevir), Olysio® (simeprevir), Victrelis® (boceprevir)) plus peginterferon plus Ribavirin; and

d. The medication is used in combination with Ribavirin; and

e. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

f. Prior authorization approval will be for 12 weeks.

7. Genotype 1, Ribavirin ineligible, treatment experienced and with compensated cirrhosis

   a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

   b. Submission of medical records (e.g., chart notes, laboratory values) documenting that the recipient has cirrhosis; and

   c. The recipient has experienced treatment failure with a previous treatment regimen that included peginterferon plus Ribavirin or an HCV protease inhibitor (e.g., Incivek® (telaprevir), Olysio® (simeprevir), Victrelis® (boceprevir)) plus peginterferon plus Ribavirin; and

   d. The recipient is Ribavirin ineligible; and

   e. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

   f. Prior authorization approval will be for 24 weeks.

8. Genotype 1, 4, 5 or 6, decompensated cirrhosis or post-liver transplant

   a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1, 4, 5 or 6 (submission of medical records e.g., chart notes, laboratory values); and

   b. One of the following:

      1. Submission of medical records (e.g., chart notes, laboratory values) documenting that the recipient has decompensated cirrhosis (e.g., Child-Pugh class B or C); or

      2. Both of the following:

         a. The recipient is a liver transplant recipient; and

         b. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

   c. The medication is used in combination with Ribavirin; and

   d. Prior authorization approval will be for 12 weeks.

9. Genotype 1,4, 5, or 6, decompensated cirrhosis, Ribavirin ineligible or prior failure of Sovaldi® or NS5A based regimen

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1, 4, 5 or 6 (submission of medical records e.g., chart notes, laboratory values); and

b. Submission of medical records (e.g., chart notes, laboratory values) documenting that the recipient has decompensated cirrhosis (e.g., Child-Pugh class B or C); and

c. One of the following:

1. The recipient is Ribavirin ineligible; or

2. Both of the following:

a. The recipient has experienced treatment failure with a previous treatment regimen that included Sovaldi® (sofosbuvir) or an NS5A inhibitor (e.g., Daklinza® (daclatasvir)); and

b. The medication is used in combination with Ribavirin; and

d. Prior authorization approval will be for 24 weeks

10. Genotype 4, treatment naïve or treatment experienced (peginterferon plus Ribavirin)

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 4 (submission of medical records e.g., chart notes, laboratory values); and

b. One of the following:

1. The recipient is treatment naïve; or

2. One of the following:

a. The recipient has experienced failure with a previous treatment regimen that included peginterferon plus Ribavirin and is without cirrhosis; or

b. Both of the following:

1. The recipient has experienced failure with a previous treatment regimen that included peginterferon plus Ribavirin and has compensated cirrhosis (Child-Pugh class A); and

2. The medication is used in combination with Ribavirin; and

c. Prior authorization approval will be for 12 weeks.

11. Genotype 5 or 6, treatment naïve or treatment experienced (peginterferon plus Ribavirin)

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 5 or 6 (submission of medical records e.g., chart notes, laboratory values); and

b. One of the following:

1. The recipient is treatment naïve; or

2. The recipient has experienced failure with a previous treatment regimen that included peginterferon plus Ribavirin; and

c. Prior authorization approval will be for 12 weeks.

d. Mavyret® (glecaprevir/pibrentasvir)

1. The following are required for all Mavyret® treatment:

a. The recipient is not receiving Mavyret® in combination with another HCV direct acting antiviral agent (e.g., Harvoni® (ledipasvir/sofosbuvir), Zepatier® (elbasvir/grazoprevir)); and

b. The medication must be prescribed by or in consultation with one of the following:

1. Hepatologist

2. Gastroenterologist

3. Infectious Disease Specialist

4. HIV Specialist (certified through the American Academy of HIV Medicine)

2. Genotype 1, 2, 3, 4, 5 or 6, treatment naïve without cirrhosis

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1, 2, 3, 4, 5 or 6 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient is treatment naïve; and

c. The recipient is without cirrhosis; and

d. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

e. Prior authorization approval will be for eight weeks.

3. Genotype 1, 2, 3, 4, 5 or 6, treatment naïve with compensated cirrhosis

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1, 2, 3, 4, 5 or 6 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient is treatment naïve; and

c. The recipient has compensated cirrhosis (Child-Pugh class A); and

d. Prior authorization approval will be for 12 weeks.

4. Genotype 1, treatment experienced (prior failure to an NS3/4A protease inhibitor), without decompensated cirrhosis

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient has experienced failure with a previous treatment regimen that included an HCV NS3/4A protease inhibitor (e.g., Incivek® (telaprevir), Olysio® (simeprevir), Victrelis® (boceprevir)); and

c. The recipient has had no previous treatment experience with a treatment regimen that included an NS5A inhibitor (e.g., Daklinza® (daclatasvir)); and

d. The recipient is without decompensated cirrhosis (Child-Pugh class B or C); and

e. Prior authorization approval will be for 12 weeks.

5. Genotype 1, treatment experienced (prior failure to an NS5A inhibitor), without decompensated cirrhosis

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient has experienced failure with a previous treatment regimen that included an NS5A inhibitor (e.g., Daklinza® (daclatasvir)); and

c. The recipient has had no previous treatment experience with a treatment regimen that included an HCV NS3/4A protease inhibitor (e.g., Incivek® (telaprevir), Olysio® (simeprevir), Victrelis® (boceprevir)); and

d. The recipient is without decompensated cirrhosis (Child-Pugh class B or C); and

e. Prior authorization approval will be for 16 weeks.

6. Genotype 3, treatment experienced (interferon or Sovaldi® based regimen), without decompensated cirrhosis

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 3 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient has experienced failure with a previous treatment regimen that included interferon, peginterferon, Ribavirin, and/or Sovaldi® (sofosbuvir); and

c. The recipient has had no previous treatment experience with a treatment regimen that included an HCV NS3/4A protease inhibitor (e.g., Incivek® (telaprevir), Olysio® (simeprevir), Victrelis® (boceprevir)) or an NS5A inhibitor (e.g., Daklinza® (daclatasvir)); and

d. The recipient is without decompensated cirrhosis (Child-Pugh class B or C); and

e. Prior authorization approval will be for 16 weeks.

7. Genotype 1, 2, 4, 5 or 6, treatment experienced (interferon or Sovaldi® based regimen), without cirrhosis

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1, 2, 4, 5 or 6 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient has experienced failure with a previous treatment regimen that included interferon, peginterferon, Ribavirin, and/or Sovaldi® (sofosbuvir); and

c. The recipient has had no previous treatment experience with a treatment regimen that included an HCV NS3/4A protease inhibitor (e.g., Incivek® (telaprevir), Olysio® (simeprevir), Victrelis® (boceprevir)) or an NS5A inhibitor (e.g., Daklinza® (daclatasvir)); and

d. The recipient is without cirrhosis; and

e. Prior authorization approval will be for eight weeks.

8. Genotype 1, 2, 4, 5 or 6, treatment experienced (interferon or Sovaldi® based regimen), with compensated cirrhosis

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1, 2, 4, 5 or 6 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient has experienced failure with a previous treatment regimen that included interferon, peginterferon, Ribavirin, and/or Sovaldi® (sofosbuvir); and

c. The recipient has had no previous treatment experience with a treatment regimen that included an HCV NS3/4A protease inhibitor (e.g., Incivek® (telaprevir), Olysio® (simeprevir), Victrelis® (boceprevir)) or an NS5A inhibitor (e.g., Daklinza® (daclatasvir)); and

d. The recipient has compensated cirrhosis (e.g., Child-Pugh class A); and

e. Prior authorization approval will be for 12 weeks.

e. Olysio® (simeprevir)

1. Submission of medical records (e.g., chart notes, laboratory values) documenting one of the following:

a. Both of the following:

1. Diagnosis of chronic hepatitis C genotype 1a; and

2. The recipient does not have the NS3 Q8K polymorphism; or

b. The recipient has a diagnosis of chronic hepatitis C genotype 1b; or

c. The recipient has a diagnosis of chronic hepatitis C genotype 4; and

2. The recipient has not experienced failure with a previous treatment regimen that includes Olysio® or other HCV NS3/4A protease inhibitors (e.g., Incivek® (telaprevir), Victrelis® (boceprevir)); and

3. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

4. The medication is used in combination with peginterferon alfa and Ribavirin; and

5. The medication must be prescribed by or in consultation with one of the following:

   a. Hepatologist

   b. Gastroenterologist

   c. Infectious Disease Specialist

   d. HIV Specialist (certified through the American Academy of HIV Medicine)

6. Genotype 1 without cirrhosis

   a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

   b. The recipient is without cirrhosis; and

   c. The medication is used in combination with Sovaldi® (sofosbuvir); and

   d. Prior authorization approval will be for 12 weeks.

7. Genotype 1 with cirrhosis

   a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

   b. Submission of medical records (e.g., chart notes, laboratory values documenting that the recipient has cirrhosis; and

   c. The medication is used in combination with Sovaldi® (sofosbuvir); and

   d. Prior authorization approval will be for 24 weeks.

f. Sovaldi® (sofosbuvir)

1. The following is required for all Sovaldi® treatment:

a. The medication must be prescribed by or in consultation with one of the following:

1. Hepatologist

2. Gastroenterologist

3. Infectious Disease Specialist

4. HIV Specialist (certified through the American Academy of HIV Medicine)

2. Genotype 1 or 4, without decompensated liver disease

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 or 4 (submission of medical records e.g., chart notes, laboratory values); and

b. The medication is used in combination with peginterferon alfa and Ribavirin; and

c. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

d. The recipient has not experienced failure with a previous treatment regimen that includes Sovaldi®; and

e. Prior authorization approval will be for 12 weeks.

3. Genotype 3, without decompensated liver disease

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 3 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient must be 18 years of age or older; or

c. Both of the following:

1. The recipient has a documented diagnosis of chronic hepatitis C virus (HCV) genotype 3 (submission of medical records e.g., chart notes, laboratory values); and

2. The recipient is 12 to 17 years of age; or both of the following:

a. The recipient weighs at least 35 kg; and

b. The recipient is less than 12 years of age; and

d. The medication is used in combination with Ribavirin; and

e. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

f. The recipient has not experienced failure with a previous treatment regimen that includes Sovaldi®; and

g. Prior authorization approval will be for 24 weeks.

4. Genotype 2, without decompensated liver disease

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 2 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient must be 18 years of age or older; or

c. Both of the following:

1. The recipient has a documented diagnosis of chronic hepatitis C genotype 2 (submission of medical records e.g., chart notes, laboratory values); and

2. The recipient is 12 to 17 years of age; or both of the following:

a. The recipient weighs at least 35 kg; and

b. The recipient is less than 12 years of age; and

d. The medication is used in combination with Ribavirin; and

e. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

f. The recipient has not experienced failure with a previous treatment regimen that includes Sovaldi®; and

g. Prior authorization approval will be for 12 weeks.

5. Genotype 1, without cirrhosis

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

b. The medication is used in combination with Olysio® (simeprevir); and

c. The recipient is without cirrhosis; and

d. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

e. The recipient has not experienced failure with a previous treatment regimen that includes Olysio® or other HCV NS3/4A protease inhibitors (e.g., Incivek® (telaprevir), Victrelis® (boceprevir)); and

f. Prior authorization approval will be for 12 weeks.

6. Genotype 1, with cirrhosis

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

b. The medication is used in combination with Olysio® (simeprevir); and

c. The recipient has cirrhosis; and

d. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

e. The recipient has not experienced failure with a previous treatment regimen that includes Olysio® or other HCV NS3/4A protease inhibitors (e.g., Incivek® (telaprevir), Victrelis® (boceprevir)); and

f. Prior authorization approval will be for 12 weeks.

7. Genotype 1

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

b. The medication is used in combination with Daklinza® (daclatasvir); and

c. The recipient has not experienced failure with a previous HCV NS5A treatment regimen (e.g., Daklinza® (daclatasvir)); and

d. One of the following:

1. The recipient is without decompensated cirrhosis and is not a liver transplant recipient; or

2. Both of the following:

a. The recipient has decompensated cirrhosis and/or is a liver transplant recipient; and

b. The medication is used in combination with Ribavirin.

e. Prior authorization approval will be for 12 weeks.

8. Genotype 3

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 3 (submission of medical records e.g., chart notes, laboratory values); and

b. The medication is used in combination with Daklinza® (daclatasvir); and

c. The recipient has not experienced failure with a previous HCV NS5A treatment regimen (e.g., Daklinza® (daclatasvir)); and

d. One of the following:

1. The recipient is without cirrhosis and is not a liver transplant recipient; or

2. Both of the following:

a. The recipient has cirrhosis (compensated or decompensated) and/or is a liver transplant recipient; and

b. The medication is used in combination with Ribavirin.

e. Prior authorization approval will be for 12 weeks.

g. Technivie® (ombitasvir, paritaprevir and ritonavir) for genotype 4

1. The recipient has a documented diagnosis of chronic hepatitis C genotype 4 (submission of medical records e.g., chart notes, laboratory values); and

2. One of the following:

a. The recipient is without cirrhosis; or

b. The recipient has compensated cirrhosis; and

3. The medication is used in combination with Ribavirin; and

4. The recipient is not receiving Technivie® in combination with another HCV direct acting agent (e.g., Harvoni® (ledipasvir), Sovaldi® (sofosbuvir), Olysio® (simeprevir)); and

5. The recipient does not have moderate to severe hepatic impairment (e.g., Child-Pugh class B or C); and

6. The medication must be prescribed by or in consultation with one of the following:

a. Hepatologist

b. Gastroenterologist

c. Infectious Disease Specialist

d. HIV Specialist (certified through the American Academy of HIV Medicine)

7. Prior authorization approval will be for 12 weeks.

h. Viekira Pak®, Viekira XR® (ombitasvir, paritaprevir, ritonavir tablets, dasabuvir tablets)

1. The following is required for all Viekira Pak®, Viekira XR® treatment:

a. The recipient has not experienced failure with a previous treatment regimen that includes HCV NS3/4A protease inhibitor (e.g., Incivek® (telaprevir), Olysio® (simeprevir), Victrelis® (boceprevir)) or an NS5A inhibitor (Daklinza® (daclatasvir)); and

b. The recipient is not receiving Viekira® in combination with another HCV direct acting antiviral agent (e.g., Harvoni® (ledipasvir), Sovaldi® (sofosbuvir), Olysio® (simeprevir)); and

c. The medication must be prescribed by or in consultation with one of the following:

1. Hepatologist

2. Gastroenterologist

3. Infectious Disease Specialist

4. HIV Specialist (certified through the American Academy of HIV Medicine)

2. Genotype 1a or mixed genotype 1, without cirrhosis and without liver transplant

   a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1a or mixed genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

   b. The recipient is without cirrhosis; and

   c. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

   d. The medication is used in combination with Ribavirin; and

   e. Prior authorization approval will be for 12 weeks.

3. Genotype 1a or mixed genotype 1, with cirrhosis and without liver transplant

   a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1a or mixed genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

   b. Submission of medical records (e.g., chart notes, laboratory values) documenting that the recipient has cirrhosis; and

   c. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

   d. The medication is used in combination with Ribavirin; and

   e. Prior authorization approval will be for 24 weeks.

4. Genotype 1b, without liver transplant

   a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1b (submission of medical records e.g., chart notes, laboratory values); and

   b. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

   c. Prior authorization approval will be for 24 weeks.

5. Genotype 1 (regardless of sub genotype), with liver transplant

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1 (submission of medical records e.g., chart notes, laboratory values); and

b. Submission of documentation that the recipient is a liver transplant recipient; and

c. Submission of medical records (e.g., chart notes or laboratory values) documenting normal hepatic function and mild fibrosis (e.g., METAVIR fibrosis score less than or equal to F2); and

d. The medication is used in combination with Ribavirin; and

e. Prior authorization approval will be for 24 weeks.

i. Vosevi® (sofosbuvir/velpatasvir/voxilaprevir)

1. The following is required for all Vosevi® treatment:

a. The recipient is without decompensated liver disease (e.g., Child-Pugh class B or C); and

b. The recipient is not receiving Vosevi® in combination with another HCV direct acting antiviral agent (e.g., Harvoni® (ledipasvir), Zepatier® (elbasvir/grazoprevir)); and

c. The medication must be prescribed by or in consultation with one of the following:

1. Hepatologist

2. Gastroenterologist

3. Infectious Disease Specialist

4. HIV Specialist (certified through the American Academy of HIV Medicine)

2. Genotype 1, 2, 3, 4, 5 or 6; without decompensated cirrhosis, prior relapse to NS5A based regimen

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1, 2, 3, 4, 5 or 6 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient is a previous relapser to an NS5A based regimen (e.g., Daklinza® (daclatasvir), Epclusa® (ledipasvir/sofosbuvir), Mavyret® (glecaprevir/pibrentasvir), Technivie® (ombitasvir/

paritaprevir/ ritonavir), Viekira® (ombitasvir/ paritaprevir/ ritonavir/dasabuvir), Zepatier® (elbasvir/grazoprevir); and

c. Submission of medical records (e.g., chart notes or laboratory values) documenting normal hepatic function and mild fibrosis (e.g., METAVIR fibrosis score less than or equal to F2); and

d. Prior authorization approval will be for 12 weeks.

3. Genotype 1a, without decompensated cirrhosis, prior relapse to sofosbuvir based regimen without an NS5A inhibitor

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1a (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient is a previous relapser to a sofosbuvir based regimen without an NS5A inhibitor; and

c. Prior authorization approval will be for 12 weeks.

4. Genotype 3, without decompensated cirrhosis, prior relapse to sofosbuvir based regimen without an NS5A inhibitor

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 3 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient is a previous relapser to a sofosbuvir based regimen without an NS5A inhibitor; and

c. Prior authorization approval will be for 12 weeks.

j. Zepatier® (elbasvir/grazoprevir)

1. The following is required for all Zepatier® treatment:

a. The recipient does not have moderate to severe hepatic impairment (e.g., Child-Pugh class B or C); and

b. The recipient is not receiving Zepatier® in combination with another HCV direct acting antiviral agent (e.g., Sovaldi® (sofosbuvir), Olysio® (simeprevir)); and

c. The medication must be prescribed by or in consultation with one of the following:

1. Hepatologist

2. Gastroenterologist

3. Infectious Disease Specialist

4. HIV Specialist (certified through the American Academy of HIV Medicine)

2. Genotype 1a, treatment naïve, or PegIFN/RBV experienced or PegIFN/RBV/protease inhibitor experienced, without NS5A polymorphisms

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1a (submission of medical records e.g., chart notes, laboratory values); and

b. One of the following:

1. The recipient is treatment naïve; or

2. The recipient has had prior failure to peginterferon alfa plus Ribavirin treatment; or

3. The recipient has had prior failure to treatment with peginterferon alfa plus Ribavirin plus an HCV NS3/4A protease inhibitor (e.g., boceprevir, simeprevir or telaprevir); and

c. Both of the following:

1. The recipient has been tested for the presence of NS5A resistance associated polymorphisms; and

2. The recipient has baseline NS5A resistance associated polymorphisms (e.g., polymorphisms at amino acid positions 28, 30, 31, or 93); and

d. The medication is used in combination with Ribavirin; and

e. Prior authorization approval will be for 16 weeks.

3. Genotype 1b, treatment naïve, or PegIFN/RBV experienced or PegIFN/RBV/protease inhibitor experienced

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 1b (submission of medical records e.g., chart notes, laboratory values); and

b. One of the following:

1. The recipient is treatment naïve; or

2. The recipient has had prior failure to peginterferon alfa plus Ribavirin treatment; or

3. Both of the following:

a. The recipient has had prior failure to treatment with peginterferon alfa plus Ribavirin plus an HCV NS3/4A protease inhibitor (e.g., boceprevir, simeprevir or telaprevir); and

b. The medication is used in combination with Ribavirin; and

c. Prior authorization approval will be for 12 weeks.

4. Genotype 4, treatment naïve

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 4 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient is treatment naïve; and

c. Prior authorization approval will be for 12 weeks.

5. Genotype 4, PegIFN/RBV experienced

a. The recipient has a documented diagnosis of chronic hepatitis C genotype 4 (submission of medical records e.g., chart notes, laboratory values); and

b. The recipient has had prior failure to peginterferon alfa plus Ribavirin; and

c. The medication is used in combination with Ribavirin; and

d. Prior authorization approval will be for 16 weeks.

2. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Hepatitis C Direct-Acting Antivirals

INTRODUCTION

- The hepatitis C virus (HCV) is an enveloped ribonucleic acid (RNA) virus that is primarily transmitted through exposure to infected blood (*Centers for Disease Control and Prevention [CDC] 2020*).
  - More than 50% of people infected with HCV will develop chronic infection *(CDC 2020).*
  - The CDC estimates that 2.4 million persons in the United States (U.S.) have chronic hepatitis C (CHC) *(CDC 2020).*
  - Chronic HCV infection can lead to the development of active liver disease, including cirrhosis and liver cancer. It is one of the most common indications for liver transplant (*CDC 2020*).
- There are 6 major genotypes of HCV, numbered 1 to 6. Genotypes are further divided into subtypes, designated by a letter (*Gower et al 2014*).
  - Genotype 1 is the most prevalent HCV genotype globally (~46% of cases), followed by genotype 3 (~22 to 30% of cases). Genotypes 2, 4, and 6 represent 22.8% of cases combined; genotype 5 represents less than 1% of cases worldwide (*Messina et al 2015, Gower et al 2014*).
  - In the U.S., the prevalence of genotype 1a, 1b, 2, 3, 4, and 6 is 46.2%, 26.3%, 10.7%, 8.9%, 6.3%, and 1.1%, respectively (*Gower et al 2014*).
- Due to the slow evolution of chronic infection, it is difficult to directly demonstrate whether treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virologic parameters. The primary goal of therapy for hepatitis C is eradication of the virus. Sustained virologic response (SVR), defined as a continued undetectable viral load 12 weeks after the completion of therapy, is the key surrogate virologic parameter that may indicate cure of HCV (*CDC 2020*).
- Obtaining an SVR is associated with a 97 to 100% chance of being HCV RNA negative during long-term follow-up. Furthermore, achieving an SVR is associated with decreased mortality, rates of hepatocellular carcinoma, liver-related complications, and the need for liver transplant. Thus, success at obtaining SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications. Some trials report SVR at 12 weeks (SVR12) in addition to or instead of at 24 weeks (SVR24). There is a high degree of concordance between SVR12 and SVR24, and SVR12 is also considered an appropriate endpoint (*Chen et al 2013*).
- Over recent years, research has focused on oral HCV agents that act directly on viral targets. These direct-acting antivirals (DAAs) are stratified into 4 major categories: NS3/4A protease inhibitors, NS5B nucleoside polymerase inhibitors, NS5B nonnucleoside polymerase inhibitors, and NS5A inhibitors (*Liang et al 2013*).
  - The first DAA-containing regimens were single-ingredient DAAs that needed to be used in combination with peginterferon (PegIFN)/ribavirin (RBV). Currently, the majority of patients can be treated with DAA agents without the need for IFN or RBV (*AASLD-IDSA 2020*).
- This review provides information on the DAAs, including: Epclusa, Harvoni, Mavyret, Sovaldi, Viekira Pak, Vosevi, and Zepatier.
  - In May 2018, AbbVie announced the discontinuation of Viekira XR (ombitasvir/paritaprevir/ritonavir and dasabuvir) and Technivie (ombitasvir/paritaprevir/ritonavir). These discontinuations were voluntary, and not due to any safety, efficacy, or quality issues. These products will no longer be available, effective January 1, 2019 (*FDA Drug Shortages 2020*).
  - Daklinza was discontinued by Bristol-Myers Squibb in January 2019. Per the manufacturer, all available supply expired on June 30, 2020 (*Direct communication with manufacturer May 18, 2020*). The discontinuation was driven by changes in routine prescribing practices and the availability of new treatments with shorter durations and reduced pill burden (*Bristol-Myers Squibb 2020)*.
- Medispan Class: Hepatitis C Agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Epclusa (sofosbuvir/velpatasvir)	✔ *
Harvoni (ledipasvir/sofosbuvir)	✔ *

Drug	Generic Availability
Mavyret (glecaprevir/pibrentasvir)	--
Sovaldi (sofosbuvir)	--
Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir)	--
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	--
Zepatier (elbasvir/grazoprevir)	--

*Authorized generics from Asegua Therapeutics (*Han 2018*).

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Epclusa* (sofosbuvir-velpatasvir)	Harvoni* (ledipasvir/sofosbuvir)	Mavyret* (glecaprevir-pibrentasvir)	Sovaldi* (sofosbuvir)	Viekira Pak (ombitasvir/paritaprevir/ritonavir/dasabuvir)	Vosevi† (sofosbuvir-velpatasvir-voxilaprevir)	Zepatier (elbasvir/grazoprevir)
Genotype 1	✔	✔	✔	✔	✔	✔	✔
Genotype 2	✔		✔	✔		✔	
Genotype 3	✔		✔	✔		✔	
Genotype 4	✔	✔	✔	✔		✔	✔
Genotype 5	✔	✔	✔			✔	
Genotype 6	✔	✔	✔			✔	

* Epclusa, Harvoni, Mavyret, and Sovaldi are the only agents approved in pediatric patients; Epclusa is indicated for the treatment of pediatric patients 6 years of age and older, or weighing at least 17 kg, with HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis, or with decompensated cirrhosis (for use in combination with RBV). Harvoni is indicated for the treatment of pediatric patients 3 years of age and older with HCV genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis, genotype 1 infection with decompensated cirrhosis (for use in combination with RBV), and genotype 1 or 4 infection in patients with liver transplantation without cirrhosis or with compensated cirrhosis (for use in combination with RBV). Mavyret is indicated for the treatment of pediatric patients 12 years of age and older, or weighing at least 45 kg, with HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis, or with genotype 1 previously treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor but not both. Sovaldi is indicated for the treatment of chronic HCV genotype 2 or 3 infection in pediatric patients 3 years of age and older without cirrhosis or with compensated cirrhosis for use in combination with RBV.

† Only approved in patients with genotypes 1, 2, 3, 4, 5, or 6 with prior failure to an NS5A inhibitor-containing regimen or patients with genotypes 1a or 3 previously treated with a sofosbuvir-containing regimen without an NS5A inhibitor.

(*Prescribing information: Epclusa 2020, Harvoni 2020, Mavyret 2020, Sovaldi 2020, Viekira Pak 2019, Vosevi 2019, Zepatier 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Epclusa

- The clinical safety and efficacy of Epclusa was evaluated in 4 pivotal phase 3 trials.
  - ASTRAL-1 was a double-blind (DB), placebo-controlled (PC), MC, randomized trial in previously treated or untreated patients who were chronically infected with HCV genotype 1, 2, 4, 5, or 6. Overall, the rate of SVR among patients who received 12 weeks of Epclusa was 99% (618/624) (95% confidence interval [CI], 98 to > 99), which was significantly superior to the prespecified performance goal of 85% ($p < 0.001$). None of the 116 patients in the placebo group had an SVR (*Feld et al 2015*).

- ASTRAL-2 was an OL, active-control (AC), MC, randomized trial comparing Epclusa for 12 weeks (n = 134) vs sofosbuvir plus RBV for 12 weeks (n = 132) in patients with genotype 2 infection. The rate of SVR12 was 99% (133/134) (95% CI, 96 to 100) among those who had received Epclusa as compared with 94% (124/132) (95% CI, 88 to 97) among those who had received sofosbuvir plus RBV (*Foster et al 2015*).
- ASTRAL-3 was an OL, AC, MC, randomized trial comparing Epclusa for 12 weeks (n = 277) vs sofosbuvir plus RBV for 24 weeks (n = 275) in patients with genotype 3 infection. The rate of SVR12 was 95% (95% CI, 92 to 98) among those who had received Epclusa, as compared with 80% (95% CI, 75 to 85) among those who had received sofosbuvir plus RBV. The overall SVR rate with Epclusa was significantly superior to that with sofosbuvir plus RBV. The strata-adjusted absolute difference was 14.8% (95% CI, 9.6 to 20.0, p < 0.001) (*Foster et al 2015*).
- ASTRAL-4 was an OL, MC, randomized trial comparing Epclusa with or without RBV for 12 weeks or Epclusa for 24 weeks in patients infected with HCV genotypes 1 through 6 and with decompensated cirrhosis. Rates of SVR12 were 83% (95% CI, 74 to 90) in patients who received Epclusa for 12 weeks, 94% (95% CI, 87 to 98) among those who received Epclusa plus RBV for 12 weeks, and 86% (95% CI, 77 to 92) among those who received Epclusa for 24 weeks. Post-hoc analyses did not detect any significant differences in rates of SVR among the 3 treatment groups (*Curry et al 2015*).

- A randomized, OL trial conducted in Spain compared 12 weeks of Epclusa to 12 weeks of Epclusa plus RBV in patients (n = 204) with HCV genotype 3 and compensated cirrhosis. SVR12 rates were 91% and 96% in the Epclusa and Epclusa plus RBV groups, respectively (*Esteban et al 2018*).
- A meta-analysis of 6 randomized controlled trials (n = 1427) found that 12 weeks of Epclusa treatment resulted in SVR12 rates of 98.2%, 99.4%, 94.7%, 99.6%, 97.1%, and 98.8% in HCV genotypes 1, 2, 3, 4, 5, and 6, respectively (*Ahmed H et al 2018[a]*).

Pediatric

- An OL study (n = 173) evaluated Epclusa for 12 weeks in patients 6 years and older with HCV genotypes 1, 2, 3, 4, or 6 without cirrhosis or with compensated cirrhosis. Of patients aged 12 to 17 years, 93% of patients with genotype 1 (71/76) and 100% of patients with genotypes 2 (6/6), 3 (12/12), 4 (2/2), and 6 (6/6) achieved SVR12. Of patients aged 6 to 11 years, 93% of patients with genotype 1 (50/54), 91% of patients with genotype 3 (10/11), and 100% of patients with genotypes 2 (2/2) and 4 (4/4) achieved SVR12 (*Epclusa prescribing information* 2020).

Harvoni

Adults

- The efficacy and safety of Harvoni were evaluated in 4 trials in genotype 1 HCV monoinfected patients, 1 trial in genotype 1 or 4 HCV/HIV-1 co-infected patients, 3 trials in genotype 4, 5, or 6 HCV monoinfected patients and 2 trials in genotype 1 or 4 HCV infected pre-transplant patients with decompensated cirrhosis (Child-Pugh B and C) or post-liver transplant.
  - ION-1 was a randomized, OL trial in treatment-naïve patients (n = 865) with genotype 1 HCV with or without cirrhosis. Patients were randomized to receive Harvoni for 12 or 24 weeks, with or without RBV. In the trial, SVR12 rates of 97 to 99% were achieved (*Afdhal et al 2014[a]*).
  - ION-2 was a randomized, OL trial in patients (n = 440) with genotype 1 HCV with or without cirrhosis who failed prior therapy with an IFN-based regimen, with or without a protease inhibitor. Patients were randomized to receive Harvoni for 12 or 24 weeks, with or without RBV. SVR12 rates of up to 99% were achieved (*Afdhal et al 2014[b]*).
  - ION-3 was a randomized, OL trial in treatment-naïve patients (n = 647) with non-cirrhotic HCV genotype 1 infection. Patients randomized to treatment with Harvoni for 8 or 12 weeks or Harvoni plus RBV for 8 weeks demonstrated SVR12 rates of 93 to 95% (*Kowdley et al 2014*).
  - ION-4 was an OL, MC trial in 335 patients evaluating 12 weeks of Harvoni in treatment-naïve and treatment-experienced cirrhotic or non-cirrhotic HIV/HCV co-infected patients. SVR12 rates were high overall (96%) with comparable rates to the HCV monoinfected population (*Naggie et al 2015*).
  - SIRIUS was a DB, MC, French study in which patients with cirrhosis who did not respond to PegIFN and RBV plus telaprevir or boceprevir, were randomized to placebo for 12 weeks followed by Harvoni plus RBV for 12 weeks (n = 77) or Harvoni plus placebo for 24 weeks (n = 78). The overall SVR12 rates were 96% and 97% for Harvoni plus RBV for 12 weeks and Harvoni plus placebo for 24 weeks, respectively (*Bourlière et al 2015*).
  - Study 1119 was an OL study evaluating Harvoni for 12 weeks in patients with genotype 4 (n = 44) or 5 infection (n = 41), with or without compensated cirrhosis. The study was conducted at 5 sites in France. There were high SVR12

rates (≥ 89%) with 12 weeks of Harvoni in all patient subgroups and similar rates for genotype 4 vs genotype 5 infection (*Abergel et al 2016*).
  - In an OL, randomized study, Harvoni for 12 weeks was compared to sofosbuvir plus RBV for 24 weeks in a cohort of Egyptian patients (n = 200) with treatment-naïve genotype 4 HCV. SVR12 was higher with Harvoni (99% vs 80% with sofosbuvir plus RBV) (*Ahmed OA et al 2018*). Another OL randomized study in Egyptian patients (n = 255) compared Harvoni and Harvoni plus RBV for 8 or 12 weeks. SVR12 rates were 95% and 90% among patients receiving 8 weeks of Harvoni and Harvoni plus RBV, respectively. The SVR12 rate for patients receiving 12 weeks of Harvoni (with or without RBV) was 98% (*Shiha et al 2019*).
  - ELECTRON-2 was an OL trial that enrolled patients from 2 centers in New Zealand. The trial evaluated Harvoni for 12 weeks in patients with genotype 6 infection (n = 25). The rate of SVR12 was 96%. The single patient who did not reach SVR12 was a patient who withdrew consent during week 8 of treatment and therefore did not receive the full course of treatment (*Gane et al 2015*).
  - SOLAR-1 and SOLAR-2 were OL, MC trials that evaluated 12 and 24 weeks of treatment with Harvoni in combination with RBV in patients with genotype 1 and 4 infection who had undergone liver transplantation and/or who had decompensated liver disease. The 2 trials were identical in study design. The SVR12 rates observed with 24 weeks of Harvoni plus RBV were similar to the SVR12 rates observed with 12 weeks of treatment. In pre-transplant patients with decompensated cirrhosis, the SVR12 rate for Harvoni plus RBV for 12 weeks was 87% (80/92). In post-transplant patients (with or without cirrhosis), the SVR12 was 93% (194/208) (*Charlton et al 2015; Manns et al 2016*).

Pediatric
- A phase 2, OL, MC study (n = 100) evaluated Harvoni for 12 weeks in patients aged 12 to 17 years with chronic HCV genotype 1 infection. Overall, 98% of patients reached SVR12. No patient had virologic failure; 2 patients who did not achieve SVR12 were lost to follow-up either during or after treatment (*Balistreri et al 2016*).
- A phase 2, OL, MC study evaluated the efficacy of Harvoni for 12 weeks (n = 89) in patients aged 6 to 11 years with chronic HCV, primarily genotype 1, infection. Treatment was given for 24 weeks for IFN-experienced patients with HCV genotype 1 and cirrhosis (n = 1); or IFN-experienced with HCV genotype 3 with or without cirrhosis (n = 2). Among patients treated for 12 weeks, SVR12 was achieved in 99% of patients (88/89); the SVR12 rate was 100% (3/3) for patients given Harvoni for 24 weeks. One patient with genotype 1a and cirrhosis who was treatment-naïve experienced virologic relapse 4 weeks after a 12-week course of treatment (*Murray et al 2018*).
- A phase 2, OL, MC study evaluated the efficacy of Harvoni for 12 weeks in patients aged 3 to 6 years with HCV genotype 1 (n = 33) or genotype 4 (n = 1). Overall, 97% of patients achieved SVR12; no patients had virological nonresponse or relapse. Only 1 patient did not achieve SVR12, who was a 3-year-old that discontinued treatment after 5 days due to “abnormal drug taste” (*Schwartz et al 2020).*

<u>Mavyret</u>

Adults
- The efficacy of Mavyret in patients who were treatment-naïve or treatment-experienced to combinations of PegIFN, RBV and/or sofosbuvir (PRS) with genotype 1, 2, 4, 5, or 6 infection without cirrhosis was studied in 5 trials using 8- or 12-week durations: ENDURANCE-1, ENDURANCE-2, ENDURANCE-4, SURVEYOR-1 (Part 2), and SURVEYOR-2 (Part 2 and Part 4).
  - ENDURANCE-1 was a randomized, MC, OL trial comparing the efficacy of 8 and 12 weeks of treatment with Mavyret in patients with genotype 1 infection with or without HIV-1 co-infection. The SVR rate was 99% (348/351) and 99.7% (351/352) in the Mavyret 8- and 12-week arms, respectively (*Mavyret prescribing information 2020, Zeuzem et al 2018*).
  - ENDURANCE-4, SURVEYOR-1, and SURVEYOR-2 were OL, MC trials evaluating the safety and efficacy of Mavyret in treatment-naïve or PRS treatment-experienced patients. ENDURANCE-4 and SURVEYOR-1 evaluated 12 weeks of Mavyret in patients with genotypes 5 and 6. The overall SVR rate was 100% (57/57). SURVEYOR-2 evaluated 8 weeks of Mavyret in patients with genotypes 2, 4, 5, or 6; the SVR rate was 98% (193/197), 93% (43/46), 100% (2/2), and 100% (10/10), respectively (*Asselah et al 2018[a], Mavyret prescribing information 2020*).
  - ENDURANCE-2 was a randomized, DB, placebo-controlled, MC study assessing the efficacy of Mavyret for 12 weeks in non-cirrhotic patients with genotype 2 HCV (n = 196). The SVR12 rate in the treatment group was 99% (*Asselah et al 2018[a]*).

- The efficacy of Mavyret in patients who were treatment-naïve or PRS treatment-experienced with genotype 1, 2, 4, 5, or 6 with compensated cirrhosis was studied in the OL, single-arm EXPEDITION-1 trial. Patients were treated with 12 weeks of Mavyret. The overall SVR rate was 99% (145/146) (*Forns et al 2017*).
- The efficacy of Mavyret in patients without cirrhosis or with compensated cirrhosis who were treatment-naïve or PRS treatment-experienced with genotype 3 infection was studied in ENDURANCE-3 and in SURVEYOR-2 (Part 3).
  - ENDURANCE-3 was a randomized, OL, AC trial in treatment-naïve patients. Patients were randomized (2:1) to either Mavyret for 12 weeks or to the combination of Sovaldi and Daklinza for 12 weeks; subsequently the trial included a third non-randomized arm with Mavyret for 8 weeks. The SVR rate for 8 weeks of Mavyret, 12 weeks of Mavyret, and 12 weeks of Sovaldi plus Daklinza was 94.9% (149/157), 95.3% (222/233), and 96.5% (111/115), respectively. The treatment difference for 12 weeks of Mavyret vs 12 weeks of Sovaldi plus Daklinza was -1.2% (95% CI, -5.6% to 3.1%). The treatment difference for 8 weeks vs 12 weeks of Mavyret was -0.4% (95% CI, -5.4% to 4.6%) (*Mavyret prescribing information 2020, Zeuzem et al 2018*).
  - SURVEYOR-2 (Part 3) was an OL trial randomizing PRS treatment-experienced patients with genotype 3 infection without cirrhosis to 12 or 16 weeks of treatment. In addition, the trial evaluated the efficacy of Mavyret in genotype 3 infected patients with compensated cirrhosis in 2 dedicated treatment arms using 12-week (treatment-naïve only) and 16-week (PRS treatment-experienced only) durations. The SVR rate was 98% (39/40) in treatment-naïve patients with cirrhosis who were treated with 12 weeks of Mavyret. The SVR rate was 96% (66/69) in PRS treatment-experienced patients, with or without cirrhosis, who were treated with 16 weeks of Mavyret (*Mavyret prescribing information 2020, Wyles et al 2017*).
  - A pooled analysis of 5 trials in patients (n = 693) with HCV genotype 3 found that treatment with Mavyret for 8 or 12 weeks achieved SVR12 in 95% of treatment-naïve patients without cirrhosis; treatment-naïve patients with cirrhosis who were treated for 12 weeks had an SVR12 rate of 97%. Treatment-experienced patients without cirrhosis achieved SVR12 rates of 90% and 96% with 12 and 16 weeks of Mavyret treatment, respectively. Treatment-experienced patients with cirrhosis achieved SVR12 rates of 94% with 16 weeks of Mavyret treatment (*Flamm et al 2019*).
- ENDURANCE-5,6 was a single-arm, OL, MC trial examining the efficacy of Mavyret in patients (n = 84) with HCV genotypes 5 and 6. Patients without cirrhosis or with compensated cirrhosis were treated with 8 or 12 weeks of Mavyret, respectively. The overall SVR12 rate was 97.6%, with 95.7% and 98.4% of patients with HCV genotype 5 and 6 infections, respectively, achieving SVR12 (*Asselah et al 2019*).
- EXPEDITION-2 was an OL study in HCV/HIV-1 co-infected patients (n = 153) evaluating Mavyret in HCV genotypes 1 through 6 with or without compensated cirrhosis for 8 or 12 weeks, respectively. Treatment-naïve and treatment-experienced patients were both included. The overall SVR12 rate was 98% (*Rockstroh et al 2018*).
- EXPEDITION-4 was an OL, single-arm, MC trial evaluating the safety and efficacy in patients with severe renal impairment (chronic kidney disease [CKD] Stages 4 and 5; 82% were on hemodialysis) with compensated liver disease (with and without cirrhosis). The study included patients with (19%) or without compensated cirrhosis (81%). The SVR rate was 98% (102/104). Of the 2 patients who failed, 1 discontinued the medication and the other was lost to follow-up *(Gane et al 2017, Mavyret prescribing information 2020).*
- EXPEDITION-8 was an OL, single-arm, MC, phase 3 trial evaluating the safety and efficacy of Mavyret once-daily for 8 weeks in 343 treatment-naïve patients with compensated cirrhosis. The SVR12 rate for genotypes 1 to 6 was 99.7% in the per-protocol population and 97.7% in the intention-to-treat population. One patient with genotype 3a infection relapsed at post-treatment week 4 (*Brown et al 2020*).
- MAGELLAN-1 was a randomized, OL trial in genotype 1- or 4-infected patients who failed a previous regimen containing an NS5A inhibitor and/or NS3/4A protease inhibitor. Due to higher rates of virologic failure and treatment-emergent drug resistance, the data did not support labeling for treatment of HCV genotype 1-infected patients who are both NS3/4A protease inhibitor and NS5A inhibitor-experienced (*Mavyret prescribing information 2020, Poordad et al 2017*).
  - In protease inhibitor-experienced patients (but NS5A inhibitor-naïve), the SVR rate was 92% (23/25) for patients treated with Mavyret for 12 weeks. In NS5A-experienced patients (but protease inhibitor-naïve), the SVR rate was 94% (16/17).
- A randomized, OL trial evaluated Mavyret in genotype 1-infected patients who failed a previous regimen containing sofosbuvir and an NS5A inhibitor. Patients were divided into 4 groups: patients without cirrhosis who received treatment with Mavyret for 12 weeks (group A; n = 78) or 16 weeks (group B; n = 49) or patients with compensated cirrhosis who received treatment with Mavyret and RBV for 12 weeks (group C; n = 21) or 16 weeks (group D; n = 29). The SVR12 rates were 90% in group A, 94% in group B, 86% in group C, and 97% in group D *(Lok et al 2019)*.

- MAGELLAN-2 was an OL trial that included treatment-naïve or treatment-experienced patients (n = 100) with chronic HCV genotype 1 through 6 who had received a liver or kidney transplant. The overall SVR12 was 98% after 12 weeks of therapy (*Reau et al 2018*). In 2018, Mavyret received approval for use in liver and kidney transplant recipients (*Mavyret prescribing information 2020*).
- An analysis of Mavyret phase 2 and 3 trials included adolescent and adult patients with HCV genotypes 1 to 6 who had a history of injection drug use (termed people who inject drugs [PWID]) and found the SVR12 rate was 98% in the former or non-PWID group compared to 89% in current or recent PWID group. The difference in SVR12 rates was reportedly due to missing data, but virologic failure rates were 2% in the current or recent PWID group compared to 1% in the former or non-PWID group. Of patients who were on medication-assisted treatment (MAT) for opioid use disorder, the SVR12 rate was 96% compared with 98% for those not on MAT. Based on these findings, no dosage adjustment of Mavyret is required for PWID or those on MAT for opioid use disorder *(Mavyret prescribing information 2020).*
- In a pooled analysis of 9 trials in patients (n = 2041) with HCV genotypes 1 through 6 without cirrhosis, treatment with Mavyret for 8 or 12 weeks resulted in SVR12 rates of 98% and 99%, respectively (*Puoti et al 2018*).
- A meta-analysis of 13 trials in 3082 patients with HCV genotypes 1 through 6 and receiving treatment with Mavyret for 8 to 12 weeks revealed an overall SVR12 rate of 97.8% (*Wang et al 2019*). Another meta-analysis of 21 trials in 4817 patients with HCV genotypes 1 through 6 receiving Mavyret for 8, 12, or 16 weeks showed an overall SVR12 rate of 97.5% *(Xu et al 2020).*
- A meta-analysis of 34 studies in 7328 patients with HCV genotype 3 showed that Mavyret resulted in higher SVR 12/24 rates (n = 244; 98.54%) compared with Epclusa with or without RBV (n = 2266; 95.08%), Vosevi (n = 117; 84.97%), or Sovaldi plus Daklinza with or without RBV (n = 4701; 95.08%) *(Zhuang et al 2020)*. However, the ability to draw conclusions from these results is limited by significant heterogeneity among treatment regimens and the small number of patients receiving Mavyret and Vosevi.

Pediatric

- DORA, a phase 2/3, OL, MC study evaluated the efficacy of Mavyret for 8 to 16 weeks in 47 patients aged 12 to 18 years of age with HCV genotypes 1 to 6 infection. Overall, 100% of patients achieved SVR12; no patients had virological nonresponse or relapse (*Jonas et al 2020*).

Sovaldi

Adults

- The clinical safety and efficacy of sofosbuvir were evaluated in 6 pivotal phase 3 trials.
  - NEUTRINO was a single-arm, OL study of Sovaldi in combination with IFN and RBV in patients infected with HCV genotype 1, 4, 5, or 6. SVR was achieved in 90% of patients at 12 weeks (*Lawitz et al 2013*).
  - FISSION was a randomized, OL, AC, non-inferiority study in patients with HCV genotype 2 or 3. Patients received treatment with Sovaldi plus RBV for 12 weeks or PegIFN plus RBV for 24 weeks. An SVR was reported in 67% of patients in both treatment groups at 12 weeks after the end of treatment (*Lawitz relapsed 2013*).
  - In POSITRON, HCV genotype 2 or 3 patients who had previously discontinued IFN therapy due to adverse events, who had a concurrent medical condition precluding therapy with an IFN, or who decided against treatment with an IFN-containing regimen were randomized to receive treatment with Sovaldi and RBV or matching placebos. Rates of SVR at 12 weeks were significantly higher in the Sovaldi treatment group compared to placebo (78 vs 0%, respectively; $p < 0.001$) (*Jacobson et al 2013*).
  - In FUSION, patients who did not achieve SVR with prior IFN therapy (relapsers or nonresponders) were randomized to receive treatment with Sovaldi and RBV for 12 or 16 weeks. Rates of SVR were 50% with 12 weeks of treatment, as compared with 73% with 16 weeks of treatment (*Jacobson et al 2013*).
  - The VALENCE trial evaluated Sovaldi in combination with RBV for the treatment of genotype 2 or 3 HCV infection in treatment-naïve patients or patients who did not achieve SVR with prior IFN-based treatment, including those with compensated cirrhosis. Rates of SVR were 93% in genotype 2 patients and 84% in genotype 3 patients (*Zeuzem et al 2014[a]*).
  - PHOTON-1 was an OL trial evaluating treatment with 12 or 24 weeks of Sovaldi in combination with RBV in genotype 1, 2, or 3 CHC patients co-infected with HIV-1. Genotype 2 and 3 patients were either treatment-naïve or experienced, whereas genotype 1 patients were treatment-naïve. Rates of SVR were similar to those observed in patients with HCV mono-infection across all genotypes (*Sulkowski et al 2014*).

Pediatric

- Study 1112 was an OL trial evaluating treatment with Sovaldi in combination with RBV in pediatric patients 12 years of age and older with genotype 2 or 3 HCV infection. Patients with HCV genotype 2 or 3 infection in the trial were treated with Sovaldi and weight-based RBV for 12 or 24 weeks, respectively. The majority of patients were treatment-naïve (83%), and 73% were infected by vertical transmission; 40% were assessed as not having cirrhosis (the remainder did not have a cirrhosis determination). SVR12 rates were 100% (13/13) for patients with genotype 2 and 97% (38/39) for genotype 3. The single patient who did not achieve SVR was lost to follow-up after achieving SVR4 (*Wirth et al 2017*).
- A phase 2, OL, MC study evaluated the efficacy of Sovaldi in patients (n = 54) aged 3 to 12 years with HCV genotype 2 for 12 weeks and in patients with genotype 3 for 24 weeks. Overall, 98% of patients achieved SVR12; no patients had virological nonresponse or relapse. Only 1 patient did not achieve SVR12, who was a 4-year-old that discontinued treatment after 3 days due to "abnormal drug taste" (*Rosenthal et al 2019*).

Vosevi

- The efficacy of Vosevi was evaluated in 2 pivotal trials in DAA-experienced patients.
  - POLARIS-1 was a randomized, DB, PC trial that evaluated 12 weeks of treatment with Vosevi compared with 12 weeks of placebo in DAA-experienced patients with genotype 1, 2, 3, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis who previously failed a regimen containing an NS5A inhibitor. Overall, 51% of patients had been previously treated with ledipasvir (the NS5A component of Harvoni). The remaining patients were treated with other NS5A inhibitors. The overall SVR rate was 96% (253/263). The SVR rate was 99% (140/142) and 93% (113/121) in patients without cirrhosis and with cirrhosis, respectively (*Bourlière et al 2017*).
  - POLARIS-4 was a randomized, OL trial that evaluated 12 weeks of treatment with Vosevi and 12 weeks of treatment with Epclusa in patients with genotype 1, 2, 3, or 4 HCV infection without cirrhosis or with compensated cirrhosis who had previously failed an HCV DAA-containing regimen that did not include an NS5A inhibitor. In the trial, prior DAA regimens contained sofosbuvir (85%) with the following: PegIFN and RBV or just RBV (69%), HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir; 15%) and investigational DAA (< 1%). The SVR12 rate was 98% (178/182) (95% CI, 95 to 99; significantly superior to the prespecified performance goal of 85% [p < 0.001]) for patients receiving Vosevi for 12 weeks. The SVR12 rate was 90% (136/151) (95% CI, 84 to 94, not significantly superior to the prespecified performance goal of 85% [p = 0.09]) for patients receiving Epclusa for 12 weeks. One patient had viral breakthrough and 14 patients relapsed (*Bourlière et al 2017*).

Viekira Pak

- Efficacy and safety of Viekira Pak were evaluated in 8 pivotal clinical trials with chronic HCV genotype 1 infection:
  - Treatment-naïve genotype 1a and 1b (SAPPHIRE-I)
  - Treatment-experienced genotype 1a and 1b (SAPPHIRE-II)
  - Treatment-experienced genotype 1b (PEARL-II)
  - Treatment-naïve genotype 1b (PEARL-III)
  - Treatment-naïve genotype 1a (PEARL-IV)
  - Treatment-naïve and -experienced genotype 1a and 1b with cirrhosis (TURQUOISE-II)
  - Treatment-naïve and -experienced genotype 1b with cirrhosis (TURQUOISE-III).
  - Treatment-naïve and -experienced genotype 1b with cirrhosis (TURQUOISE-IV)
- SAPPHIRE-I and SAPPHIRE-II were MC, randomized, DB, PC trials. Patients were randomized to Viekira Pak plus RBV for 12 weeks or placebo. Patients in the placebo treatment arm received placebo for 12 weeks, after which they received OL Viekira Pak plus RBV for 12 weeks (*Feld et al 2014, Zeuzem et al 2014[b]*).
  - In SAPPHIRE-I (n = 631), SVR12 was achieved in 96.2% (95% CI, 94.5 to 97.9) of patients receiving Viekira Pak with RBV. This rate was non-inferior and superior to the historical control rate with telaprevir plus PegIFN/RBV.
  - In SAPPHIRE-II (n = 394), SVR12 was achieved in 96.3% (95% CI, 94.2 to 98.4) of patients receiving Viekira Pak with RBV. This rate was non-inferior and superior to the historical control rate among patients who had previously been treated with PegIFN/RBV and who received retreatment with telaprevir plus PegIFN/RBV.
- In PEARL-II (n = 186), patients without cirrhosis were randomized to receive OL Viekira Pak with or without RBV for 12 weeks of treatment (*Andreone et al 2014*).
  - Rates of SVR12 were 96.6% (95% CI, 92.8 to 100) with Viekira Pak plus RBV and 100% (95% CI, 95.9 to 100) with Viekira Pak alone. Rates of SVR in both treatment groups were non-inferior and superior to the historical rate for telaprevir plus PegIFN/RBV in comparable treatment-experienced patients.

- Non-inferiority of treatment with Viekira Pak alone compared to Viekira Pak plus RBV was met (treatment difference in SVR12 rates, 3.4% [95% CI, -0.4 to 7.2]).

- PEARL-III and PEARL-IV were MC, DB, PC trials. Patients without cirrhosis were randomized to receive Viekira Pak with or without RBV for 12 weeks of treatment (*Ferenci et al 2014*).
  - In PEARL-III (n = 419), treatment with Viekira Pak resulted in SVR12 rates of 99.5% (95% CI, 98.6 to 100) with RBV and 99% (95% CI, 97.7 to 100) without RBV in patients with genotype 1b infection.
  - In PEARL-IV (n = 305), treatment with Viekira Pak resulted in SVR12 rates of 97% (95% CI, 93.7 to 100) with RBV and 90.2% (95% CI, 86.2 to 94.3) without RBV in patients with genotype 1a infection.
- The OL TURQUOISE-II trial (n = 380) enrolled patients with compensated cirrhosis (Child-Pugh A) or liver scarring with few to no outward symptoms who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients were randomized to receive Viekira Pak in combination with RBV for 12 or 24 weeks of treatment. Patients who previously failed therapy with a treatment regimen that included a DAA were excluded (*Poordad et al 2014*).
  - Patients who received 12 weeks of treatment had an SVR12 response of 91.8% (97.5% CI, 87.6 to 96.1).
  - Those patients who received 24 weeks of treatment achieved an SVR12 rate of 95.9% (97.5% CI, 92.6 to 99.3).
  - Rates of SVR12 in the 12- and 24-week treatment groups were non-inferior and superior to the historical rate with telaprevir plus PegIFN/RBV among patients with HCV genotype 1 infection and cirrhosis. The difference in the rates of SVR between the 2 treatment groups was not significant.
- The OL TURQUOISE-III trial (n = 60) enrolled genotype 1b patients with compensated cirrhosis who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients were randomized to receive Viekira Pak for 12 weeks. SVR12 was achieved in all patients enrolled in the study (*Feld et al 2016*).
- The OL TURQUOISE-IV trial (n = 36) enrolled genotype 1b patients in Russia and Belarus with compensated cirrhosis who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients received Viekira Pak plus RBV for 12 weeks. SVR12 was achieved in all patients enrolled in the study (*Isakov et al 2018*).
- Safety and efficacy of Viekira Pak were also evaluated in liver transplant patients and in patients with HCV genotype 1 co-infected with HIV-1.
  - CORAL-I was a phase 2, OL trial in HCV genotype 1 liver transplant recipients who were at least 12 months post transplantation with mild fibrosis (Metavir score < F2). Patients received treatment with Viekira Pak with RBV for 24 weeks. Of the 34 patients enrolled, 33 achieved an SVR12, for a rate of 97% (95% CI, 85 to 100) (*Kwo et al 2014*).
  - TURQUOISE-I was a phase 3, randomized, OL trial in 63 patients with treatment-naïve or -experienced HCV genotype 1 infection who were co-infected with HIV-1. Patients on a stable antiretroviral therapy regimen were treated for 12 or 24 weeks with Viekira Pak in combination with RBV. SVR12 rates were 91% for patients with HCV genotype 1a infection and 100% for those with genotype 1b infection (*Wyles et al 2014*).

Zepatier

- The safety and efficacy of Zepatier were evaluated in 7 pivotal clinical trials including patients with genotype 1 or 4 infection. A small number of patients with other HCV genotypes were also included in the clinical trials; however, Zepatier is only indicated for genotypes 1 and 4.
  - C-EDGE TN was a DB, PC, MC, randomized study in treatment-naïve patients with genotype 1, 4, or 6 infection. Of the 316 patients receiving Zepatier for 12 weeks, 95% (95% CI, 92 to 97) achieved SVR12. SVR12 was achieved in 97% (95% CI, 90 to 100) of cirrhotic patients and 94% (95% CI, 90 to 97) of noncirrhotic patients (*Zeuzem et al 2015*).
  - C-EDGE CO-INFECTION was an OL, MC trial in treatment-naïve patients with genotype 1, genotype 4, and genotype 6 infection who were co-infected with HIV. All patients (n = 218) received Zepatier for 12 weeks. In the overall population, 96% achieved SVR12 (95% CI, 92.9 to 98.4), exceeding the historical reference rate of 70% (*Rockstroh et al 2015*).
  - C-SURFER was a DB, PC, MC, randomized study, evaluating Zepatier for 12 weeks in patients with genotype 1 infection with CKD stage 4 to 5. Of the 122 patients receiving Zepatier, 6 were excluded from the modified full analysis set population for reasons other than virologic failure. Of the 116 remaining patients, 115 achieved SVR12, a rate better than the historical control rate of 45% ($p < 0.001$) (*Roth et al 2015*).
  - C-SCAPE was an OL, randomized study that evaluated the efficacy of Zepatier for 12 weeks, with or without RBV, in patients with genotype 4, 5, or 6 infection. In patients with genotype 4 infection, SVR12 was achieved in 100% (10/10) of patients receiving Zepatier with RBV vs 90% (9/10) in patients receiving Zepatier alone (*Brown et al 2015, Brown et al 2018*).

- C-EDGE TE was an OL, MC, randomized study evaluating 12 or 16 weeks of Zepatier, with or without RBV in patients with genotype 1, 4, or 6 HCV infection and previous treatment with Peg IFN/RBV. SVR12 was achieved in 92.4% (97/105) receiving Zepatier alone for 12 weeks, 94.2% (98/104) receiving Zepatier plus RBV for 12 weeks, 92.4% (97/105) receiving Zepatier alone for 16 weeks, and 97.2% (103/106) receiving Zepatier plus RBV (*Kwo et al 2017*).
- C-SALVAGE was an OL, MC study evaluating Zepatier plus RBV for 12 weeks in patients (n = 79) with genotype 1 infection who failed a regimen containing PegIFN/RBV and another DAA. SVR12 was achieved in 96% (95% CI, 89.3 to 99.2) of patients. The 3 patients not achieving SVR12 had a past history of virologic failure (*Forns et al 2015*).
- C-CORAL was a randomized, DB, PC study evaluating Zepatier for 12 weeks in treatment-naïve patients (n = 489) with genotype 1, 4, or 6 HCV infection. SVR12 was achieved in 94.4% of patients receiving Zepatier. SVR12 rates of 98.2%, 91.9%, and 66.7% were seen in patients with genotype 1b, 1a, and 6 infections, respectively (*Wei et al 2019*).

- A meta-analysis of 8 trials (n = 1297) found an overall SVR rate of 96.6% with Zepatier treatment in patients with genotype 1 HCV (*Ahmed H et al 2018[b]*).
- In a pooled analysis of clinical trial data, treatment-naïve and treatment-experienced patients with genotype 4 HCV infection (n = 155) had SVR12 rates of 96.4% (treatment-naïve) and 88.6% (treatment-experienced) after 12 or 16 weeks of Zepatier with or without RBV (*Asselah et al 2018[b]*).

CLINICAL GUIDELINES

- In order to provide healthcare professionals with timely guidance, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management (*AASLD-IDSA 2020*).
  - Recommended regimens are those that are favored for most patients in a given group, based on optimal efficacy, favorable tolerability and toxicity profiles, and duration.
  - The guidance also lists alternative regimens, which are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens. For a listing of alternative regimens, refer to the web-based guidance for full details.
- For the general genotype 1 population, the guidance recommends 4 different regimens considered to have comparable efficacy: Epclusa, Harvoni, Mavyret, and Zepatier. The level of evidence and treatment duration depend on the genotype 1 subtype, prior treatment status (naïve or experienced), and the presence of cirrhosis.
- The guidance recommends Epclusa and Mavyret for patients with genotype 2 or 3 infection.
- The guidance recommends Epclusa, Harvoni, Mavyret, and Zepatier for the treatment of genotype 4 infection. The guidance recommends Epclusa, Harvoni, and Mavyret for treatment of genotype 5 and 6.
- The guidance provides recommendations for several unique patient populations, including patients who have failed prior therapy with DAAs, co-infection with HIV/HCV, decompensated cirrhosis, recurrent HCV infection in the post-transplant setting, renal impairment, pregnancy, and children. Some key recommendations include:
  - Epclusa, Harvoni (listed as an alternative for patients with compensated cirrhosis), and Mavyret are recommended for genotype 1 patients with prior failure to HCV NS3/4A protease inhibitors. Epclusa (genotype 1b), Mavyret (regardless of genotype 1 subtype), and Vosevi (genotype 1a) are recommended for patients with prior failure to sofosbuvir-containing regimens.
  - Vosevi is recommended in genotype 1, 3, 4, 5, or 6 patients with prior failure to an NS5A inhibitor-containing regimen.
  - Mavyret + Sovaldi + RBV or Vosevi + RBV are recommended in patients with or without compensated cirrhosis who failed Vosevi monotherapy. Vosevi monotherapy or Mavyret + Sovaldi + RBV are recommended in patients with or without compensated cirrhosis who failed Mavyret monotherapy.
  - Sovaldi-based regimens (ie, Epclusa, Harvoni) are recommended for patients with decompensated cirrhosis.
  - HIV/HCV-co-infected patients should be treated and re-treated the same as patients without HIV infection, after recognizing and managing interactions with antiretroviral medications.
  - For patients with renal impairment, the guideline states no dose adjustment is required when using recommended DAA regimens. For kidney transplant recipients, Harvoni (genotypes 1, 4, 5 or 6), Mavyret, or Epclusa are recommended for treatment-naïve patients.
  - Mavyret (regardless of genotype) may be used in treatment-naive adolescents ages 12 years and older and Harvoni (genotype 1, 4, 5, or 6) may be used in treatment-naïve children ages 3 years and older. Children older than 3 years should receive treatment with DAAs available for a child's age group.

SAFETY SUMMARY

- Due to the DAAs used in combination therapy with PegIFN and RBV, all contraindications to those 2 medications (PegIFN and RBV) also apply to the class. This includes a contraindication for use in pregnancy due to the RBV component.
- Mavyret is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C) or with a history of prior hepatic decompensation and when coadministered with atazanavir and rifampin.
- Viekira Pak is contraindicated in patients with:
  - Moderate to severe hepatic impairment (Child-Pugh B and C) due to the risk of potential toxicity.
  - Known hypersensitivity to ritonavir (eg, toxic epidermal necrolysis or Stevens-Johnson syndrome).
  - Concomitant use of drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
  - Concomitant use of drugs that are moderate or strong inducers of CYP3A.
  - Concomitant use of drugs that are strong inducers or strong inhibitors of CYP2C8
- Vosevi is contraindicated in patients with rifampin coadministration.
- Zepatier is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) or with a history of hepatic decompensation. It is also contraindicated with organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors, strong inducers of CYP3A, and efavirenz.
- Key warnings and precautions for the DAAs include:
  - Serious symptomatic bradycardia may occur in patients taking amiodarone and sofosbuvir in combination with another DAA (eg, Epclusa, Harvoni, Vosevi).
  - Viekira Pak carries a risk of hepatic decompensation and hepatic failure in patients with cirrhosis.
  - Mavyret and Vosevi may cause hepatic decompensation and/or failure, including a fatal outcome, in patients with advanced liver disease.
- Clearance of HCV infection may affect the safe and effective use of concomitant medications (eg, hypoglycemia due to diabetes medications, INR fluctuations in patients on warfarin).
- Overall, DAA combination therapies are well tolerated and discontinuations due to adverse events are not common.
  - The most common adverse reactions observed with each treatment regimen listed below include:
    - Epclusa: headache and fatigue
    - Epclusa and RBV in patients with decompensated cirrhosis: fatigue, anemia, nausea, headache, insomnia, and diarrhea
    - Harvoni: fatigue, headache, and asthenia
    - Mavyret: headache and fatigue
    - Sovaldi in combination with RBV: fatigue and headache
    - Sovaldi in combination with PegIFN alfa and RBV: fatigue, headache, nausea, insomnia, and anemia
    - Viekira Pak with RBV: fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia
    - Viekira Pak without RBV: nausea, pruritus, and insomnia
    - Vosevi: headache, fatigue, diarrhea, and nausea
    - Zepatier: fatigue, headache, and nausea
    - Zepatier with RBV: anemia and headache

- In October 2016, the FDA announced that a new *Boxed Warning* would be added to all DAAs for HCV infection, regarding the risk of hepatitis B virus (HBV) reactivation. This *Boxed Warning* was based on case reports submitted to the FDA and from the published literature of HCV/HBV co-infected patients treated with DAAs from November 2013 to July 2016 (*FDA 2016*).
  - HBV can become reactivated in any patient who has a current or previous infection with HBV and is treated with DAAs. In a few cases, HBV reactivation in patients treated with DAAs resulted in serious liver problems or death.
  - The *Boxed Warning* was added to the labeling for all of the DAAs in February 2017. The warning directs healthcare providers to test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. HCV/HBV co-infected patients should be monitored for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Appropriate patient management for HBV infection should be initiated as clinically indicated.
  - In August 2019, the FDA announced that worsened liver function or liver failure may develop in patients with moderate to severe liver impairment (Child-Pugh B or C) using Mavyret, Zepatier, or Vosevi. Liver failure or

decompensation typically occurred during the first 4 weeks of therapy. Stopping the medication resolved or improved symptoms (*FDA 2019*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Epclusa (sofosbuvir/velpatasvir)	Tablet	Oral	Once daily	• No dosage adjustment is necessary in patients with renal impairment, including dialysis. *Duration of therapy:* • 12 weeks
Harvoni (ledipasvir/sofosbuvir)	Tablet, oral pellets	Oral	Once daily	• No dosage adjustment is necessary in patients with renal impairment, including dialysis. *Duration of therapy:* • 12 to 24 weeks
Mavyret (glecaprevir/pibrentasvir)	Tablet	Oral	Once daily	• Contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) or with a history of prior hepatic administration *Duration of therapy:* • 8 to 16 weeks
Sovaldi (sofosbuvir)	Tablet, oral pellets	Oral	Once daily; must be used in combination with RBV ± PegIFN	• Safety and efficacy have not been established in patients with severe renal impairment. *Duration of therapy:* • 12 to 24 weeks
Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir)	Tablets	Oral	Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening)	• Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). *Duration of therapy:* • 12 to 24 weeks
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	Tablet	Oral	Once daily	• No dosage adjustment is necessary in patients with renal impairment, including dialysis. • Not recommended in patients with moderate or severe hepatic impairment

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				(Child-Pugh B or C) or a history of prior hepatic decompensation. *Duration of therapy:* • 12 weeks
Zepatier (elbasvir/grazoprevir)	Tablet	Oral	Once daily	• Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms is recommended prior to initiation of treatment with Zepatier to determine dosage regimen and duration. • No dosage adjustment is necessary in patients with renal impairment, including dialysis. • Contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) or with a history of hepatic decompensation. *Duration of therapy:* • 12 to 16 weeks

See the current prescribing information for full details

CONCLUSION

- Hepatitis C is a disease affecting primarily the liver that results from infection with the hepatitis C virus. Long-term complications include cirrhosis and hepatocellular carcinoma. Hepatitis C is the leading indication for liver transplant.
- Success at obtaining an SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications.
- PegIFN-free, DAA combination regimens, such as Epclusa, Harvoni, Mavyret, and Zepatier have become the standard of care for the treatment of genotype 1 infection. There is a lack of head-to-head trial data available comparing these regimens, but they are considered to have comparable efficacy and safety for treating the general genotype 1 population (*AASLD-IDSA 2020*).
- The DAA fixed-dose combination products approved and recommended for the treatment of genotype 2 and 3 infection are Mavyret and Epclusa (*AASLD-IDSA 2020*).
- Similar to genotype 1, several DAA combination regimens have demonstrated high SVR rates for genotype 4 infection. Epclusa, Harvoni, Mavyret, and Zepatier are recommended by the AASLD-IDSA guidance (*AASLD-IDSA 2020*).
- Data are limited for treatment of genotype 5 and 6 infection; however, Epclusa, Harvoni, and Mavyret are approved by the FDA and supported by the AASLD-IDSA guidance (*AASLD-IDSA 2020*).
- Of the combination products, Epclusa and Harvoni are the preferred treatment options in patients with decompensated cirrhosis (Child-Pugh B and C). Mavyret, Zepatier, and Epclusa are recommended for patients with advanced kidney disease (*AASLD-IDSA 2020*).

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Prior Authorization Guideline

Guideline Name CGRP Products

1 . Criteria

Product Name: Ajovy, Emgality	
Diagnosis	Episodic Migraine
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient is 18 years of age or older

AND

2 - The recipient has a documented diagnosis of episodic migraines, having 4-14 migraine days per month, but not more than 14 headache days per month

AND

3 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

AND

4 - The recipient must meet TWO of the following:

4.1 One of the following:

- The recipient has a documented history of failure (after at least a two-month trial) or intolerance to Elavil (amitriptyline) or Effexor (venlafaxine)
- The recipient has a contraindication to both Elavil (amitriptyline) and Effexor (venlafaxine)

OR

4.2 One of the following:

- The recipient has documented history of failure (after at least a two-month trial) or intolerance to Depakote/Depakote ER (divalproex) or Topamax (topiramate)
- The recipient has a contraindication to both Depakote/Depakote ER (divalproex) and Topamax (topiramate)

OR

4.3 One of the following:

- The recipient has a history of failure (after at least a two month trial) or intolerance to one of the following beta blockers: atenolol, propranolol, nadolol, timolol or metoprolol
- The recipient has a contraindication to all of the following beta blockers: atenolol, propranolol, nadolol, timolol and metoprolol

Product Name: Aimovig	
Diagnosis	Episodic Migraine
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient is 18 years of age or older

AND

2 - The recipient has a documented diagnosis of episodic migraines, having 4-14 migraine days per month, but not more than 14 headache days per month

AND

3 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

AND

4 - The recipient must meet TWO of the following:

4.1 One of the following:

- The recipient has a documented history of failure (after at least a two-month trial) or intolerance to Elavil (amitriptyline) or Effexor (venlafaxine)
- The recipient has a contraindication to both Elavil (amitriptyline) and Effexor (venlafaxine)

OR

4.2 One of the following:

- The recipient has documented history of failure (after at least a two-month trial) or intolerance to Depakote/Depakote ER (divalproex) or Topamax (topiramate)
- The recipient has a contraindication to both Depakote/Depakote ER (divalproex) and Topamax (topiramate)

OR

4.3 One of the following:

- The recipient has a history of failure (after at least a two month trial) or intolerance to one of the following beta blockers: atenolol, propranolol, nadolol, timolol or metoprolol
- The recipient has a contraindication to all of the following beta blockers: atenolol, propranolol, nadolol, timolol and metoprolol

Product Name: Aimovig, Ajovy, Emgality

Diagnosis	Episodic Migraine
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient must have documented positive clinical response to CGRP therapy, demonstrated by a reduction in headache frequency and/or intensity

AND

2 - The use of acute migraine medications (e.g., NSAIDs, triptans) has decreased since the start of CGRP therapy

AND

3 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

Product Name: Ajovy, Emgality	
Diagnosis	Chronic Migraine
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient is 18 years of age or older

AND

2 - The recipient has a diagnosis of chronic migraines

AND

3 - The recipient has greater than or equal to 15 headache days per month, of which at least eight must be migraine days for at least three months

AND

4 - The recipient has been considered for MOH and potentially offending medication(s) have been discontinued

AND

5 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

AND

6 - The recipient must meet TWO of the following:

6.1 One of the following:

- The recipient has a documented history of failure (after at least a two-month trial) or intolerance to Elavil (amitriptyline) or Effexor (venlafaxine)
- The recipient has a contraindication to both Elavil (amitriptyline) and Effexor (venlafaxine)

OR

6.2 One of the following:

- The recipient has documented history of failure (after at least a two-month trial) or intolerance to Depakote/Depakote ER (divalproex) or Topamax (topiramate)
- The recipient has a contraindication to both Depakote/Depakote ER (divalproex) and Topamax (topiramate)

OR

6.3 One of the following:

- The recipient has a history of failure (after at least a two month trial) or intolerance to one of the following beta blockers: atenolol, propranolol, nadolol, timolol or metoprolol
- The recipient has a contraindication to all of the following beta blockers: atenolol, propranolol, nadolol, timolol and metoprolol

Product Name: Aimovig

Diagnosis	Chronic Migraine
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient is 18 years of age or older

AND

2 - The recipient has a diagnosis of chronic migraines

AND

3 - The recipient has greater than or equal to 15 headache days per month, of which at least eight must be migraine days for at least three months

AND

4 - The recipient has been considered for MOH and potentially offending medication(s) have been discontinued

AND

5 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

AND

6 - The recipient must meet TWO of the following:

6.1 One of the following:

- The recipient has a documented history of failure (after at least a two-month trial) or intolerance to Elavil (amitriptyline) or Effexor (venlafaxine)
- The recipient has a contraindication to both Elavil (amitriptyline) and Effexor (venlafaxine)

OR

6.2 One of the following:

- The recipient has documented history of failure (after at least a two-month trial) or intolerance to Depakote/Depakote ER (divalproex) or Topamax (topiramate)
- The recipient has a contraindication to both Depakote/Depakote ER (divalproex) and Topamax (topiramate)

OR

6.3 One of the following:

- The recipient has a history of failure (after at least a two month trial) or intolerance to one of the following beta blockers: atenolol, propranolol, nadolol, timolol or metoprolol
- The recipient has a contraindication to all of the following beta blockers: atenolol, propranolol, nadolol, timolol and metoprolol

Product Name: Aimovig, Ajovy, Emgality	
Diagnosis	Chronic Migraine
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient must have documented positive clinical response to CGRP therapy, demonstrated by a reduction in headache frequency and/or intensity

AND

2 - The use of acute migraine medications (e.g., NSAIDs, triptans) has decreased since the start of CGRP therapy

AND

3 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

AND

4 - The recipient continues to be monitored for MOH

Product Name: Emgality	
Diagnosis	Episodic Cluster Headaches
Approval Length	3 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient has a diagnosis of episodic cluster headache

AND

2 - The recipient has experienced at least two cluster periods lasting from seven days to 365 days, separated by pain-free periods lasting at least three months

AND

3 - The recipient is 18 years of age or older

AND

4 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

Product Name: Emgality	
Diagnosis	Episodic Cluster Headaches
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient must have a documented positive response to the Emgality therapy, demonstrated by a reduction in headache frequency and/or intensity

AND

2 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

Product Name: Nurtec ODT, Ubrelvy	
Diagnosis	Acute Migraine
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Recipient must have a diagnosis of acute migraine with or without aura

AND

2 - Recipient is 18 years of age or older

AND

3 - The prescribed dose will not exceed two doses per migraine and treating no more than eight migraine episodes per 30 days

AND

4 - The recipient has had at least one trial and failure of a triptan agent

AND

5 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

Product Name: Nurtec ODT, Ubrelvy	
Diagnosis	Acute Migraine
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient must have a documented positive response to therapy

AND

2 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

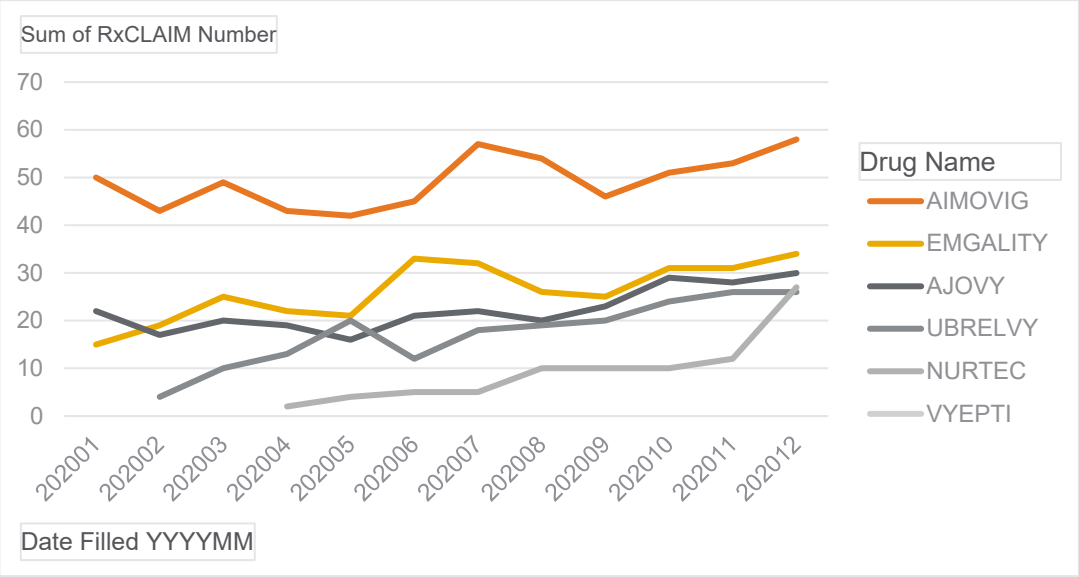
Nevada Medicaid

CGRP Receptor Antagonists

Fee for Service

January 1, 2020 – December 31, 2020

Drug Name	Members	Count of Claims	Total Days Supply	Total Quantity
AIMOVIG	92	591	18,629	703
AJOVY	57	267	9,207	458
EMGALITY	62	314	10,464	377
NURTEC	41	85	2,284	794
UBRELVY	53	192	4,099	2,188
VYEPTI	1	1	90	1



S. Anti-Migraine Medications

Therapeutic Class: Serotonin 5-HT1 receptor agonists (triptans)
Last Reviewed by the DUR Board: July 25, 2019

Therapeutic Class: Calcitonin Gene-Related Peptide (CGRP) Receptor Inhibitor Medications
Last Reviewed by the DUR Board: April 30, 2020

Serotonin 5-HT1 receptor agonists commonly referred to as "triptans" and CGRP Receptor Inhibitor medications or anti-migraine medications are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Serotonin 5-HT1 Receptor Agonists (triptans)

   a. An approved prior authorization is required for any prescription exceeding the quantity limits. Approval for additional medication beyond these limits will be considered only under the following circumstances:

      1. The recipient's current medication history documents the use of prophylactic medications for migraine headache or the medical provider agrees to initiate such therapy which includes beta-blockers, tricyclic antidepressants, anticonvulsants, Selective Serotonin Reuptake Inhibitors (SSRIs) and/or calcium channel blockers; or

      2. The medical provider is aware of and understands the implications of daily use and/or overuse of triptans and agrees to counsel the patient on this issue in an effort to taper the quantity of triptan medication required monthly.

         a. Recipient's current medication history must NOT have Monoamine Oxidase (MAO) Inhibitors present for approval of Imitrex® (sumitriptan), Maxalt® (rizatriptan) or Zomig® (zolmitriptan).

         b. Recipients whose current medication history indicates the use of propranolol will NOT be granted prior authorization of Maxalt® (rizatriptan) 10mg tablet or 10mg orally disintegrating tablet.

         c. Prior authorization will NOT be given to patients with ischemic heart disease.

   b. Prior Authorization Guidelines:

      1. Approval for exceeding the quantity limits on tripitans will be provided for a two month time period.

      2. The prior authorization must be initiated by the prescriber. The approved prior authorization must be available if requested.

3. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

2. Calcitonin Gene-Related Peptide (CGRP) Receptor Inhibitor Medications

a. Approval will be given if the following criteria are met and documented:

1. CGRP General Criteria

a. The recipient must have one of the following:

1. Both the following:

a. The recipient has a diagnosis of episodic migraines; and

b. The recipient has four to 14 migraine days per month, but not more than headache days per month; or

2. All the following:

a. The recipient has a diagnosis of chronic migraines; and

2. The recipient has greater than or equal to 15 headache days per month, of which at least eight must be migraine days for at least three months; and

c. The recipient has been considered for medication overuse headache (MOH) and potentially offending medication(s) have been discontinued; and

3. The recipient is 18 years of age or older; and

4. The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist; and

5. The recipient must meet two of the following:

a. One of the following:

1. The recipient has documented history of failure (after at least a two-month trial) or intolerance to Elavil® (amitriptyline) or Effexor® (venlafaxine); or

2. The recipient has a contraindication to Elavil® (amitriptyline) and Effexor® (venlafaxine); or

b. One of the following:

1. The recipient has documented history of failure (after at least a two-month trial) or intolerance to Depakote®/Depakote® ER (divalproex sodium) or Topamax® (topiramate); or

2. The recipient has a contraindication to both Depakote®/Depakote® ER (divalproex sodium) and Topamax® (topiramate); or

c. One of the following:

1. The recipient has documented history of failure (after at least a two-month trial) or intolerance to one of the following beta blockers:

a. Atenolol; or

b. Propranolol; or

c. Nadolol; or

d. Timolol; or

e. Metoprolol; or

2. The recipient has a contraindication to all the following beta blockers:

a. Atenolol; or

b. Propranolol; or

c. Nadolol; or

d. Timolol; or

e. Metoprolol.

b. Recertification Request:

1. The recipient must have a documented positive response to Aimovig® (erenumab-aooe), Ajovy® (fremanezumab-

vfrm) or Emgality® (galcanezumab-gnlm) therapy, demonstrated by a reduction in headache frequency and/or intensity; and

2. The recipient has had a decrease in use of acute migraine medications (e.g. NSAIDs, triptans) since the start of CGRP therapy; and

3. The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist; and

4. For chronic migraine only: The recipient continues to be monitored for MOH.

c. Prior Authorization Guidelines:

1. Initial request will be approved for six months.
2. Recertification request will be approved for 12 months.

3. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

2. Acute Migraines

a. Ubrelvy® (ubrogepant)

1. Approval will be given if all the following criteria are met and documented:

a. Recipient must have a diagnosis of acute migraine with or without aura; and

b. Recipient is 18 years of age or older; and

c. The prescribed dose will not exceed two doses per migraine and treating no more than eight migraine episodes per 30 days; and

d. The recipient has had at least one trial and failure of triptan agent; and

e. The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist.

2. Recertification Request:

a. The recipient must have a documented positive response to the Ubrelvy® therapy; and

b. The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist.

3. Prior Authorization Guidelines:

a. Initial request will be approved for six months.

b. Recertification request will be approved for 12 months.

c. Prior authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

3. Episodic Cluster Headache

a. Emgality® (galcanezumab-gnlm)

1. Approval will be given if all the following criteria are met and documented

a. The recipient has a diagnosis of episodic cluster headache; and

b. The recipient has experienced at least two cluster periods lasting from seven days to 365 days, separated by pain-free periods lasting at least three months.

c. The recipient is 18 years of age or older.

d. The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist.

2. Recertification Request:

a. The recipient has documented positive response to Emgality® therapy, demonstrated by a reduction in headache frequency and/or intensity; and

b. The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialits.

3. Prior Authorization Guidelines:

a. Initial request will be approved for three months.

b. Recertification request will be approved for 12 months.

c. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

Therapeutic Class Overview
Calcitonin gene related peptide (CGRP) inhibitors

INTRODUCTION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period (*International Headache Society [IHS] 2018, Starling et al 2015).*
  - The goals for treatment of migraine are to reverse or stop the progression of a migraine attack. The goals for preventive treatment are to reduce the frequency, severity and duration of a migraine (*American Headache Society [AHS] 2019, Katsarava 2012*).
- The International Classification of Headache Disorders (ICHD) includes both cluster headache and migraine as part of a group of primary headache disorders (*IHS 2018*):
  - Chronic migraine is defined as ≥ 15 headache days per month for > 3 months with the features of migraine headache for at least 8 mean migraine days per month (MMD). The most common cause of symptoms suggestive of chronic migraine is medication overuse. According to the ICHD, around 50% of patients apparently with chronic migraine revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed with chronic migraine. In most clinical trials, migraine that is not chronic (ie, < 15 headache days per month) is considered to be episodic migraine, although the condition is not clearly defined in the ICHD.
  - Cluster headache is defined as ≥ 5 attacks lasting 15 to 180 minutes every other day to 8 times a day with severe unilateral orbital, supraorbital, and/or temporal pain. Episodic cluster headache attacks occur for a period of 7 days to 1 year and are separated by pain-free periods lasting at least 3 months. Common symptoms include nasal congestion, rhinorrhea, conjunctival injection and/or lacrimation, eyelid edema, sweating (forehead or face), miosis, ptosis, and/or a sense of restlessness or agitation.
- Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women. Migraines have a global prevalence of 15 to 18% and are a leading cause of disability worldwide. Chronic migraine is estimated to occur in 2 to 8% of patients with migraine, whereas episodic migraine occurs in more than 90% of patients. Cluster headache is rare compared to other primary headache disorders. It is estimated to have a prevalence of 0.1% within the general population (*Global Burden of Disease Study [GBD] 2016, Hoffman et al 2018, Lipton et al 2016, Ljubisavljevic et al 2019, Manack et al 2011*).
- Treatments for migraines and cluster headache are divided into acute and preventive therapies. Evidence and reputable guidelines clearly delineate appropriate therapies for episodic migraine treatment and prophylaxis; options stretch across a wide variety of therapeutic classes and are usually oral therapies. For the prevention of migraines, treatment options include oral prophylactic therapies, injectable prophylactic therapies, and neuromodulator devices. Oral prophylactic migraine therapies have modest efficacy, and certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. For the treatment of acute migraine, options include triptans, ergots, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, small molecule CGRP inhibitors, and a 5-hydroxytryptamine (5-HT)$_{1F}$ receptor agonist. For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy, and suboccipital steroid injections are most effective for prevention (*American Migraine Foundation [AMF] 2020, Marmura et al 2015, Robbins et al 2016, Silberstein et al 2012, Simpson et al 2016)*.
- The calcitonin gene-related peptide (CGRP) pathway is important in pain modulation and the Food and Drug Administration (FDA) has approved 6 CGRP inhibitors for prevention or treatment of migraine/headache disorder(s). Erenumab-aooe is a fully human monoclonal antibody, which potently binds to the CGRP receptor in a competitive and reversible manner with greater selectivity than to other human calcitonin family receptors. Fremanezumab-vfrm, eptinezumab-jjmr, and galcanezumab-gnlm are humanized monoclonal antibodies that bind to the CGRP ligand and block its binding to the receptor. Rimegepant and ubrogepant are small molecule oral CGRP receptor antagonists (*Dodick et al 2018[b], Edvinsson 2017, Goadsby et al 2017, Sun et al 2016, Tepper et al 2017*).
  - Two CGRP inhibitors known as the “gepants,” telcagepant and olcegepant, were previously investigated. In 2009, Merck withdrew the FDA application for telcagepant because of elevated liver enzymes and potential liver toxicity

observed with chronic use, which was likely related to the chemical structure of the compound. The manufacturer of olcegepant also ceased pursuing FDA approval; however, the manufacturer did not explicitly state the rationale. It has been widely speculated that olcegepant development ceased due to limitations associated with administration as an intravenous (IV)-only product (*Edvinsson et al 2017, Walker et al 2013*). No substantial issues with liver toxicity have been observed in trials with the currently marketed CGRP inhibitors.
  - Additional CGRP inhibitors early in their development include zavegepant, the first intranasally administered CGRP inhibitor, and atogepant, another oral CGRP inhibitor (*Biohaven 2020*, *Staines 2019*).
  - In April 2019, Teva announced that it would not pursue development of fremanezumab-vfrm for an episodic cluster headache indication due to results from the ENFORCE trial (*Teva Pharmaceuticals press release 2019*). Erenumab-aooe and eptinezumab-jjmr are not currently under clinical investigation for the indication of cluster headache (*Clinicaltrials.gov 2020*).
- Medispan class: Migraine products – monoclonal antibodies; Calcitonin gene−related peptide (CGRP) receptor antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aimovig (erenumab−aooe)	–
Ajovy (fremanezumab-vfrm)	–
Nurtec ODT (rimegepant sulfate)	–
Emgality (galcanezumab-gnlm)	–
Ubrelvy (ubrogepant)	–
Vyepti (eptinezumab-jjmr)	–

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	**Aimovig** (erenumab−aooe)	**Ajovy** (fremanezumab-vfrm)	**Emgality** (galcanezumab-gnlm)	**Nurtec ODT** (rimegepant)	**Ubrelvy** (ubrogepant)	**Vyepti** (eptinezumab-jjmr)
Acute treatment of migraine with or without aura in adults	-	-	-	✔*	✔*	-
Preventive treatment of migraine in adults	✔	✔	✔	-	-	✔
Treatment of episodic cluster headache in adults	-	-	✔	-	-	-

* Limitation of use: Not indicated for the preventive treatment of migraine.
(*Prescribing information: Aimovig 2020, Ajovy 2020, Emgality 2019, Nurtec ODT 2020, Ubrelvy 2019, Vyepti 2020)*

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Rimegepant ODT has been studied as acute therapy in approximately 1466 patients in 1 Phase 3 trial of episodic migraine (with or without aura) patients and in 1 unpublished long-term safety trial. Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet formulation were considered supportive for approval; 2 trials

included approximately 2348 patients with episodic migraine, and 1 dose-ranging study included 885 patients randomized to 6 dose groups of rimegepant, sumatriptan 100 mg, or placebo.

- Ubrogepant has been studied as acute therapy in approximately 3360 patients across 2 trials in patients with 2 to 8 migraines/month with moderate to severe pain intensity either with or without aura.
- Eptinezumab-jjmr has been studied in approximately 2019 patients across 2 trials in patients with episodic or chronic migraine subtypes for prevention, with data available in published formats.
- Erenumab-aooe has been studied as preventive therapy in approximately 2500 patients across 4 trials in patients with episodic or chronic migraine subtypes and 1 open-label extension (OLE) trial, with data available in published formats.
- Fremanezumab-vfrm has been studied as preventive therapy in approximately 2005 patients across 3 trials in patients with episodic or chronic migraine subtypes and 1 OLE, with data available in published formats. In fremanezumab-vfrm trials, the definition of a headache or migraine day for the primary endpoint required a consecutive 2 hour (episodic) or 4 hour (chronic) duration of pain, compared to other CGRP inhibitor trials that required a duration of ≥ 30 minutes.
- Galcanezumab-gnlm has been studied as preventive therapy in approximately 2886 patients across 3 trials in patients with episodic or chronic migraine subtypes and 1 long-term safety trial with unpublished data to 1 year. The efficacy and safety of galcanezumab-gnlm was evaluated for treatment in one 8-week study with 106 adults with episodic cluster headache (maximum of 8 attacks/day).
- The definition of the primary and secondary endpoints differed in the prevention of episodic and chronic migraine trials. Additional differences included, but were not limited to, co-morbid conditions, concomitant medications, a requirement of stable doses of migraine prevention medication (if co-administered) for certain durations, and the definitions of headache, migraine headache, and migraine day. Some CGRP inhibitor trials allowed patients to receive concomitant preventive migraine medication during treatment. Also, some chronic migraine trials allowed for the inclusion of patients with medication overuse headache.

Prevention of episodic migraine

Eptinezumab-jjmr

- PROMISE-1 was a double-blind (DB), placebo-controlled (PC), multi-center (MC), Phase 3 trial in which adults with a history of episodic migraine were randomized to receive placebo (n = 222), eptinezumab-jjmr 100 mg (n = 221), or eptinezumab-jjmr 300 mg (n = 222) every 3 months for 12 months. The primary efficacy endpoint was the change in MMD from baseline to week 12. Eptinezumab-jjmr 100 mg and 300 mg significantly reduced MMDs across weeks 1 to 12 compared with placebo (placebo, −3.2; 100 mg, −3.9, p = 0.02; 300 mg, −4.3, p = 0.0001). The odds for a 50% reduction in MMD were approximately 1.7 to 2.2 times higher with eptinezumab-jjmr than placebo. Of note, the endpoints underwent a testing hierarchy and were not significant for 50% migraine responder rates in the 100 mg dose group (*Ashina et al 2020, Vyepti [dossier] 2020).*

Erenumab-aooe

- The STRIVE trial was a 6-month, DB, PC, MC, Phase 3 trial in which 955 patients with episodic migraine were randomized to placebo (n = 319), erenumab-aooe 70 mg (n = 317), or erenumab-aooe 140 mg (n = 319) once monthly. The primary endpoint was the change in mean MMD from baseline to months 4 to 6, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.4; 95% confidence interval [CI], −1.9 to −0.9; p < 0.001) and erenumab−aooe 140 mg (mean change vs placebo, −1.9; 95% CI, −2.3 to −1.4; p < 0.001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 16.7%; odds ratio [OR], 2.13; difference for 140 mg vs placebo, 23.4%; OR, 2.81). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 70 mg vs placebo, −0.9; difference for 140 mg vs placebo, −1.4) (*Goadsby et al 2017*). Data after 1 year of treatment found sustained efficacy in episodic migraine (*Goadsby et al 2020[a]*).
- The ARISE trial was a 12-week, DB, PC, MC, Phase 3 trial in which 577 patients with episodic migraine were randomized to placebo (n = 291) or erenumab-aooe 70 mg (n = 286) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.0; 95% CI, −1.6 to −0.5; p < 0.001). Compared to placebo, erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference, 10.2%; OR, 1.59). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −0.6) (*Dodick et al 2018[a]*).

- The LIBERTY trial was a 12-week, DB, PC, MC, Phase 3b trial in which 246 patients with episodic migraine who failed 2 to 4 prior preventive migraine treatments were randomized to placebo (n = 125) or erenumab-aooe 140 mg (n = 121) once monthly. The primary endpoint was the proportion of patients with ≥ 50% reduction in MMD from baseline to the last 4 weeks of DB treatment (weeks 9 to 12), which erenumab−aooe significantly increased over placebo (difference, 16.6%; OR, 2.73; 95% CI, 1.43 to 5.19; p = 0.002). Compared to placebo, 5.9% more patients treated with erenumab−aooe 140 mg reported a 100% reduction in MMD, or migraine cessation. Erenumab-aooe 140 mg/month compared with placebo significantly reduced the MMD (difference, −1.61; 95% CI, −2.70 to −0.52; p = 0.004). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −1.73) (*Reuter et al 2018*).

Fremanezumab-vfrm

- The HALO-EM trial was a 12-week, DB, PC, MC, Phase 3 trial in which 875 patients with episodic migraine were randomized to placebo (n = 294), fremanezumab-vfrm 225 mg once monthly (n = 290), or fremanezumab-vfrm 675 mg once quarterly (n = 291). The primary endpoint was the change in mean MMD, which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −1.5; 95% CI, −2.0 to −0.9; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.3; 95% CI, −1.8 to −0.7; p < 0.001). Of note, HALO-EM was powered to detect a 1.6-day difference in the MMD between the fremanezumab-vfrm and placebo groups, but effect sizes resulted in a 1.5-day reduction for the fremanezumab-vfrm monthly dosing group and a 1.3-day reduction for the fremanezumab-vfrm quarterly dosing group. Although the threshold was not reached, a minimal clinically important difference has not been established for this particular outcome. Compared to placebo, greater MMD reductions were also observed in patients who were prescribed fremanezumab-vfrm 225 mg (mean change vs placebo, −1.3) and 675 mg (mean change vs placebo, −1.1) as monotherapy. Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 225 mg vs placebo, 19.8%; OR, 2.36; difference for 675 mg vs placebo, 16.5%; OR, 2.06). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −1.4; difference for 675 mg vs placebo, −1.3) (*Dodick et al 2018[b]*). Data after 1 year of treatment found sustained efficacy in episodic migraine (*Goadsby et al 2020[b]*).
- FOCUS was a DB, PC, Phase 3b trial that evaluated 838 patients with episodic (39%) or chronic migraine (61%) who had previously not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, approximately 40% were classified as having episodic migraines and randomized to fremanezumab-vfrm 225 mg administered monthly with no loading dose (n = 110/283), fremanezumab-vfrm 675 mg administered quarterly (n = 107/276), or placebo (n = 112/279) for 12 weeks. Failure was defined as no clinically meaningful improvement after at least 3 months of therapy at a stable dose, as per the treating physician's judgment, discontinuation because of adverse events that made treatment intolerable, or treatment contraindicated or unsuitable for the preventive treatment of migraine for the patient. At baseline, the MMD was approximately 14.2 days and the MMHD (of at least moderate severity) was 12.6 days. For the overall population, the MMD reduction over 12 weeks was 0.6 (standard error [SE], 0.3) days for placebo, 4.1 (SE, 0.34) days for the monthly fremanezumab-vfrm group (least squares mean difference [LSMD] vs placebo, -3.5; 95% CI, -4.2 to -2.8 days; p < 0.0001), and 3.7 (SE, 0.3) for days for the quarterly fremanezumab-vfrm group (LSMD vs placebo, -3.1; 95% CI, -3.8 to -2.4 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.1 days for both dose groups (fremanezumab-vfrm monthly: LSMD, -3.1; 95% CI, -4.0 to -2.3 days; fremanezumab-vfrm quarterly: LSMD, -3.1; 95% CI, -3.9 to -2.2 days; p < 0.0001 for both). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 34% in both the quarterly and monthly fremanezumab-vfrm groups vs 9% with placebo (p < 0.0001). Only the monthly fremanezumab-vfrm arm achieved a ≥ 75% sustained responder rate that was statistically different from placebo (OR, 8.6; 95% CI, 2.0 to 37.9; p = 0.0045). Adverse events were similar for placebo and fremanezumab-vfrm. Serious adverse events were reported in 4 (1%) of 277 patients with placebo, 4 (1%) of 285 with monthly fremanezumab-vfrm, and 2 (< 1%) of 276 with quarterly fremanezumab-vfrm (*Ferrari et al 2019*).

Galcanezumab-gnlm

- The EVOLVE-1 and EVOLVE-2 trials were 6-month, DB, PC, MC, Phase 3 trials in 858 and 915 patients with episodic migraine, respectively. Patients were randomized to placebo (EVOLVE-1, n = 433; EVOLVE-2, n = 461), galcanezumab-gnlm 120 mg once monthly (EVOLVE-1, n = 213; EVOLVE-2, n = 231), or galcanezumab-gnlm 240 mg once monthly (EVOLVE-1, n = 212; EVOLVE-2, n = 223). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The EVOLVE-1 trial included a North American population and the EVOLVE-2 trial

included a global population. The primary endpoint was the change in mean monthly migraine headache days (MMHD) (*Stauffer et al 2018, Skljarevski et al 2018*).
  - In EVOLVE-1, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −1.9; 95% CI, −2.5 to −1.4; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.8; 95% CI, −2.3 to −1.2; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.7%; OR, 2.64; difference for 240 mg vs placebo, 22.3%; OR, 2.50). Compared to placebo, 9.4% more patients treated with galcanezumab-gnlm 120 mg and 9.4% more treated with galcanezumab-gnlm 240 mg reported a 100% reduction in MMHD, or migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.6) (*Stauffer et al 2018*).
  - In EVOLVE-2, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.0; 95% CI, −2.6 to −1.5; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.4 to −1.4; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.0%; OR, 2.54; difference for 240 mg vs placebo, 21.0%; OR, 2.34). Compared to placebo, 5.8% more patients treated with galcanezumab-gnlm 120 mg and 8.1% more treated with galcanezumab-gnlm 240 mg reported migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.7) (*Skljarevski et al 2018*).
  - In an analysis of persistence for patients with episodic migraine, 41.5 and 41.1% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (21.4%; p < 0.001). Approximately 6% of galcanezumab-gnlm-treated patients maintained ≥ 75% response all 6 months vs 2% of placebo-treated patients. Few galcanezumab-gnlm-treated patients maintained 100% response for all 6 months (< 1.5%) (*Förderreuther et al 2018*).
- CONQUER was a DB, PC, Phase 3b trial that evaluated 462 patients with episodic (58%) or chronic migraine (42%) who had previously not responded to 2 to 4 classes of migraine preventive medications for 12 weeks. All galcanezumab-gnlm patients were administered a 240 mg loading dose, then 120 mg per month. Failure was defined as discontinuation owing to no response or inadequate response, or safety or tolerability event. At baseline, the MMHD was approximately 13.2 days with 9.3 in the episodic migraine group and 18.7 in the chronic migraine group. For the overall population, the MMHD reduction over 12 weeks was 1.0 (SE, 0.3) days for placebo, 4.1 (SE, 0.3) days for the monthly galcanezumab-gnlm group (LSMD, -3.1; 95% CI, -3.9 to -2.3 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMHD reduction over 12 weeks was 2.6 days for the galcanezumab-gnlm monthly group (95% CI, -3.4 to -1.7 days; p < 0.0001). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 41.8% in the monthly galcanezumab-gnlm group vs 17.1% with placebo (p < 0.0001). Compared to placebo, the monthly galcanezumab-gnlm arm achieved a statistically significant improvement of ≥ 75% sustained responder (3.7 vs 18.4%; OR, 5.9; 95% CI, 2.4 to 14.6; p = 0.0001) and 100% sustained responder (0 vs 7.7%; p < 0.0001). Treatment-emergent adverse events were similar for placebo and galcanezumab-gnlm (53 vs 51%). Serious adverse events were reported in 2 patients (1%) of each of the groups (*Mulleners et al 2020*).

Prevention of chronic migraine

Eptinezumab-jjmr

- The PROMISE-2 trial was a 12-week, DB, PC, MC, Phase 3 trial in which 1121 patients with chronic migraine were randomized to placebo (n = 366), eptinezumab-jjmr 100 mg (n = 356), or eptinezumab-jjmr 300 mg (n = 350) once every 12 weeks (or quarterly). The primary endpoint was the change in mean MMD. Treatment with eptinezumab 100 and 300 mg was associated with significant reductions in MMDs across weeks 1 to 12 compared with placebo (placebo −5.6; 100 mg −7.7, p < 0.0001; 300mg −8.2, p < 0.0001). The odds for a 50% reduction in MMD were approximately 2.1 to 2.4 times higher with eptinezumab-jjmr than placebo (*Lipton et al 2020*). Updated data from PROMISE-2 demonstrated similar responses at 24 weeks as were observed at 12 weeks (*Silberstein et al 2020*).

Erenumab-aooe

- Erenumab-aooe was studied in a 12−week, DB, PC, MC, Phase 2 trial in which 667 patients with chronic migraine were randomized to placebo (n = 286), erenumab−aooe 70 mg (n = 191), or erenumab−aooe 140 mg (n = 190) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg and erenumab−aooe 140 mg (mean change for both doses vs placebo, −2.5; 95% CI, −3.5 to

−1.4; p < 0.0001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 17%; OR, 2.2; difference for 140 mg vs placebo, 18%; OR, 2.3). Both erenumab−aooe 70 mg (difference, −1.9) and erenumab−aooe 140 mg (difference, −2.6) significantly reduced the mean acute migraine−specific medication days; however, the higher 140 mg dose had a greater reduction numerically over placebo and reductions may be dose−dependent (*Tepper et al 2017*).
  - An analysis of patient reported outcomes found patients with chronic migraine had clinically relevant improvements across a range of measures. Improvements were observed at month 3 for all endpoints regardless of erenumab−aooe dose, and minimally important clinical differences were achieved for certain measures with the erenumab−aooe 140 mg dose (*Lipton et al 2019[b]*).

Fremanezumab-vfrm

- Fremanezumab-vfrm was studied in a 12-week, DB, PC, MC, Phase 3 trial, HALO-CM, in which 1130 patients with chronic migraine were randomized to placebo (n = 375), fremanezumab-vfrm 225 mg once monthly (n = 379), or fremanezumab-vfrm 675 mg once quarterly (n = 376). Patients in the fremanezumab-vfrm 225 mg group received a loading dose of 675 mg at the first injection only. The primary endpoint was the change in mean headache days (MHD), which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −2.1; SE, ± 0.3; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.8; SE, ± 0.3; p < 0.001). Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MHD (difference for 225 mg vs placebo, 22.7%; OR, 2.73; difference for 675 mg vs placebo, 19.5%; OR, 3.13). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −2.3; difference for 675 mg vs placebo, −1.8) (*Silberstein et al 2017*). Data after 1 year of treatment found sustained efficacy in chronic migraine (*Goadsby et al 2020[b]*).
- FOCUS was previously described as including 838 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 61% were diagnosed with chronic migraine and were randomized to fremanezumab-vfrm 675 mg administered quarterly (n = 169/276), a fremanezumab-vfrm 675 mg loading dose followed by 225 mg administered monthly (n = 173/283), or placebo (n = 167/279). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.8 days for the fremanezumab-vfrm monthly group and 3.2 days for the fremanezumab-vfrm quarterly group (fremanezumab-vfrm monthly: LSMD, -3.8; 95% CI, -4.8 to -2.8 days; fremanezumab-vfrm quarterly: LSMD, -3.2; 95% CI, -4.2 to -2.2 days; p < 0.0001 for both) (*Ferrari et al 2019*).

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in a 12-week, DB, PC, MC, Phase 3 trial, REGAIN, in which 1113 patients with chronic migraine were randomized to placebo (n = 558), galcanezumab-gnlm 120 mg once monthly (n = 278), or galcanezumab-gnlm 240 mg once monthly (n = 277). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The primary endpoint was the change in MMHD, which favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.1; 95% CI, −2.9 to −1.3; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.7 to −1.1; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 12.2%; OR, 2.10; difference for 240 mg vs placebo, 12.1%; OR, 2.10). Compared to placebo, 0.2% more patients treated with galcanezumab-gnlm 120 mg and 0.8% more treated with galcanezumab-gnlm 240 mg reported migraine cessation; this was not statistically different for either dose group. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −2.5; difference for 240 mg vs placebo, −2.1) (*Detke et al 2018*).
  - In an analysis of persistence for patients with chronic migraine, 29% of galcanezumab-gnlm-treated patients maintained ≥ 30% response all 3 months compared to 16% of placebo-treated patients. A total of 16.8 and 14.6% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (6.3%; p < 0.001). Few patients maintained ≥ 75% response (< 3%) (*Förderreuther et al 2018*).
- CONQUER was previously described as including 462 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 42% were diagnosed with chronic migraine and were randomized to galcanezumab-gnlm 240 mg loading dose followed by 120 mg administered monthly (n = 95/193), or placebo (n = 98/193). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMHD reduction over 12 weeks was 3.7 days for the galcanezumab-gnlm monthly group (95% CI, -5.2 to -2.2 days; p < 0.0001) (*Mulleners et al 2020*).

Treatment of episodic cluster headache

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in an 8-week, DB trial, in which 106 patients with episodic cluster headache were randomized to placebo (n = 57) or galcanezumab-gnlm 300 mg once monthly (n = 49). A total of 90 (85%) patients completed the DB phase. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen (APAP), and NSAIDs during the study. At baseline, patients had a mean of 17.5 headache attacks/week, maximum of 8 attacks/day, minimum of 1 attack every other day, and at least 4 attacks during the prospective 7-day baseline period. For the primary endpoint, galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency during weeks 1 to 3 vs placebo (-8.7 vs -5.2 attacks; p = 0.036). Galcanezumab-gnlm was also associated with a significantly greater proportion of responders (≥ 50% reduction in weekly cluster headache attack frequency) at week 3 (71.4 vs 52.6%; p = 0.046). Adverse events did not differ between groups, except for a significant increase in the incidence of injection-site pain with galcanezumab-gnlm treated patients (8 vs 0%; p = 0.04) (*Clinicaltrials.gov [NCT02397473] 2020, Emgality prescribing information 2019, Goadsby et al 2019*).

Treatment of acute migraine (with or without aura)

Rimegepant ODT

- Rimegepant ODT was evaluated in a Phase 3, DB, MC, PC, randomized controlled trial (RCT) in 1466 patients (modified intention to treat, n = 1351) with migraine with or without aura. Patients were randomized to placebo (n = 682) or rimegepant ODT 75 mg (n = 669) and were not allowed a second dose of study treatment. Rescue medications allowed 2 hours post-dose included aspirin, ibuprofen, naproxen (or any other type of NSAID), APAP up to 1000 mg/day, antiemetics (eg, metoclopramide or promethazine), or baclofen. Approximately 14% of patients were taking preventive medications for migraine at baseline. The co-primary endpoints were pain freedom and most bothersome symptom (MBS) freedom at 2 hours post-dose. Among patients randomized, 92.2% were included in the efficacy analysis and 93.8% in the safety analysis (*Croop et al 2019, Nurtec ODT [dossier] 2020, Nurtec ODT prescribing information 2020*).
  - The percentage of patients achieving headache pain freedom and MBS freedom 2 hours after a single dose was statistically significantly greater in patients who received rimegepant ODT compared to those who received placebo.
    - *Pain-free at 2 hours*: 21.2% for rimegepant ODT 75 mg vs 10.9% for placebo (p < 0.0001)
    - *MBS-free at 2 hours*: 35.1% for rimegepant ODT 75 mg vs 26.8% for placebo (p = 0.0009)
  - Out of the 21 secondary endpoints tested hierarchically, significant results were achieved for the first 19 endpoints. Those endpoints that were considered not significant included freedom from nausea at 2 hours post-dose, and pain relapse from 2 to 48 hours.
  - The most common adverse events were nausea and urinary tract infection. No serious adverse events were reported.
- Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet (non-ODT) formulation were considered supportive for approval.
  - A MC, DB, dose-ranging trial using an adaptive design was conducted to determine an effective and tolerable dose range of rimegepant for the acute treatment of migraine. A total of 885 adults with migraine with or without aura were randomized to 1 of 6 rimegepant dose groups (10, 25, 75, 150, 300, or 600 mg), sumatriptan 100 mg, or placebo. It was found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (31.4% [n = 27/86] vs 15.3% [n = 31/203]; p = 0.002). The most common adverse events were nausea, vomiting, and dizziness. No treatment-related serious AEs were reported (*Marcus et al 2014*).
  - A MC, DB, PC, Phase 3 trial (n = 1072 in efficacy analysis) evaluating rimegepant vs placebo for acute migraine treatment found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (19.6 vs 12.0%; absolute difference, 7.6%; 95% CI, 3.3 to 11.9; p < 0.001). In addition, the proportion of patients who were free from their MBS 2 hours post-dose was significantly higher with rimegepant 75 mg oral tablet compared with placebo (37.6 vs 25.2%; absolute difference, 12.4%; 95% CI, 6.9 to 17.9; p < 0.001). Nausea and urinary tract infection were the only AEs reported in > 1% of the patients in the rimegepant and placebo groups. A serious adverse event associated with rimegepant was back pain (n = 1) (*Lipton et al 2019[c]*, *Nurtec ODT [dossier] 2020*).

- A MC, DB, PC, Phase 3 trial (n = 1084 in efficacy analysis) evaluating rimegepant vs placebo for acute migraine treatment found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (19.2 vs 14.2%; p = 0.03). In addition, the proportion of patients who were free from their MBS 2 hours post-dose was significantly higher with rimegepant 75 mg oral tablet compared with placebo (36.6 vs 27.7%; p = 0.002). Nausea and dizziness were the most common adverse events reported in the rimegepant and placebo treatment groups, respectively. Serious adverse events were reported in 2 patients treated with rimegepant and 1 patient treated with placebo (*Lipton et al 2018 [poster], Nurtec ODT [dossier] 2020*).

Ubrogepant

- Ubrogepant was evaluated in 2 Phase 3, PC, DB trials (ACHIEVE I and II), in which 3358 patients (ACHIEVE I, n = 1672; ACHIEVE II, n =1686) were randomized to take 1 dose of placebo (n = 1122), ubrogepant 50 mg (n = 1118), or ubrogepant 100 mg (n = 557) (100 mg was evaluated in the ACHIEVE I trial only, and a 25 mg group was included in the ACHIEVE II trial only [n = 561]). Patients had 2 to 8 migraines/month with moderate to severe pain intensity in the past 3 months either with or without aura and had a history of migraine for ≥ 1 year. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. At baseline, 23% of patients were taking preventive medications for migraine, and approximately 23 to 27% were insufficient triptan responders. In ACHIEVE I, 79% were included in the efficacy analysis and 86% in the safety analysis, and in ACHIEVE II, 91.7% had a qualifying migraine event and 88% were included in the analysis (*Dodick et al 2019, Lipton et al 2019[a], Ubrelvy prescribing information 2019*).
  - Compared to placebo, significant improvements were demonstrated for the co-primary endpoints of pain freedom and the MBS freedom at 2 hours post-dose in the ubrogepant arms. MBS was a collection of selective, self-identified symptoms (ie, photophobia, phonophobia, or nausea). The following differences from placebo were demonstrated:
    - *Pain-free at 2 hours*: 7.4% (p = 0.002) and 7.5% (p = 0.007) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.4% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
    - *MBS-free at 2 hours*: 10.8% and 11.5% (p < 0.001 for both) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.9% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
  - The incidence of photo- and phonophobia was reduced following administration. Significantly more patients maintained pain freedom for 2 to 24 hours post-dose in the ubrogepant 100 mg arm (difference from placebo, 6.8%; p = 0.002) and the 50 mg arm for ACHIEVE II only (6.2%; p = 0.005).
  - In ACHIEVE I, the most common adverse events included nausea (1.5 to 4.7%), somnolence (0.6 to 2.5%), and dry mouth (0.6 to 2.1%). In ACHIEVE II, the most common adverse events within 48 hours were nausea (≤ 2.5% for all arms) and dizziness (≤ 2.1% for all arms). No serious adverse events or adverse events leading to discontinuation were reported 48 hours after the initial dose. In ACHIEVE II, the serious adverse events at 30 days included appendicitis, spontaneous abortion, pericardial effusion, and seizure.

CLINICAL GUIDELINES

Acute treatment of migraine

- The American Headache Society (AHS) published updated consensus statement guidelines for migraine in 2018. The AHS recommends the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or dihydroergotamine (DHE) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans, but recommend that non-oral routes be used when severe nausea or vomiting is present. Overall, the AHS designated the following drugs as having efficacy (*AHS 2019*):
  - Established efficacy:
    - Triptans
    - Ergotamine derivatives
    - NSAIDs (aspirin, diclofenac, ibuprofen, naproxen)
    - Opioids (butorphanol, although use is not recommended)
    - Combination medications
  - Probably effective
    - Ergotamine or other forms of DHE
    - NSAIDs (ketoprofen, ketorolac intramuscular or IV, flurbiprofen)

    - Magnesium IV
    - Isometheptene compounds
    - Combination medications (codeine/APAP, tramadol/APAP)
    - Antiemetics (prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)
  - The AHS recommends that rimegepant and ubrogepant may have a role in patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans, as determined by either a validated acute treatment patient reported outcome questionnaire or healthcare provider attestation. Coverage should be provided until ≥ 2 attacks are treated to determine efficacy and tolerability.
    - Other agents have had more established efficacy and safety relative to the newly FDA-approved migraine agents.
- There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan or therapy (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]*).
- In 2019, the American Academy of Neurology (AAN) and the AHS published a guideline on the acute treatment of migraine in children and adolescents. The guideline states that there is evidence to support the efficacy of ibuprofen, APAP (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents (*Oskoui et al 2019[a]*).
  - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Prevention of migraine

- According to the AAN/AHS evidence−based guideline update on the pharmacologic treatment for episodic migraine prevention in adults, the following medications are effective preventive treatment options (see Appendix A for a definition of classifications) (*Silberstein et al 2012*):
  - Level A (established efficacy and > 2 Class I trials):
    - Antiepileptic drugs: divalproex sodium, sodium valproate, and topiramate
    - Beta blockers: metoprolol, propranolol, and timolol
    - Triptans (for menstrual related migraine [MRM]): for short−term prophylaxis, frovatriptan
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Antidepressants: amitriptyline and venlafaxine
    - Beta blockers: atenolol and nadolol
    - Triptans (for MRM): for short−term prophylaxis, naratriptan and zolmitriptan
  - Level C (possibly effective and 1 Class II trial):
    - Angiotensin−converting enzyme (ACE) inhibitors: lisinopril
    - Angiotensin II receptor blockers (ARBs): candesartan
    - Alpha agonists: clonidine and guanfacine
    - Antiepileptic drugs: carbamazepine
    - Beta blockers: nebivolol and pindolol
    - Antihistamines: cyproheptadine
- The AAN recommends onabotulinumtoxin A as an effective treatment option that should be offered for chronic migraine. However, onabotulinumtoxin A is considered ineffective for the treatment of episodic migraines and should not be offered. There is insufficient evidence to compare the effectiveness of botulinum neurotoxin A with that of oral prophylactic topiramate (*Simpson et al 2016*).
- In 2019, the AAN/AHS published a guideline on the preventive treatment of migraine in pediatric patients. The guideline states that the majority of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. The guidelines make the following statements and recommendations for initial therapy (see Appendix B for a definition of classifications) (*Oskoui et al 2019[b]*):
  - It is possible that cognitive behavioral therapy (CBT) alone is effective in migraine prevention.
  - There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents.
  - Acknowledging the limitations of currently available evidence, use of short-term treatment trials (a minimum of 2 months) may be warranted in those who could benefit from preventive treatment (Level B).
  - Consider amitriptyline combined with cognitive behavioral therapy (CBT) (inform of the potential adverse events, including risk of suicide) (Level B).

- Consider topiramate (Level B). Inform of side effects including decreased efficacy when combined with oral contraceptives and the teratogenic effect in patients of childbearing potential (Level A). In patients of childbearing potential, daily folic acid is recommended (Level A).
- Consider propranolol (Level B).
  - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Cluster headache

- According to the AHS evidence-based guidelines for the treatment of cluster headache, there are a number of effective treatment options (AAN classifications were used for grading; see Appendix A for definitions) (*Robbins et al 2016*).
- For acute therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Certain triptans: sumatriptan subcutaneous and zolmitriptan nasal spray
    - Oxygen
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Certain triptans: sumatriptan nasal spray and zolmitriptan oral
    - Sphenopalatine ganglion stimulation
  - Level C (possibly effective and 1 Class II trial):
    - Cocaine/lidocaine nasal spray
    - Octreotide subcutaneous
- For preventive therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Suboccipital steroid injection
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Civamide nasal spray (not marketed in the US)
  - Level C (possibly effective and 1 Class II trial):
    - Lithium
    - Verapamil
    - Warfarin
    - Melatonin

SAFETY SUMMARY

- Ubrogepant is contraindicated with concomitant use of strong CYP3A4 inhibitors.
- Eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, and rimegepant are contraindicated in patients with serious hypersensitivity to the active ingredient or any of the excipients. Mild to moderate hypersensitivity reactions (eg, rash, dyspnea, pruritus, urticaria) were reported in trials. Cases of anaphylaxis and angioedema have been reported post-marketing. Delayed serious hypersensitivity has occurred with rimegepant. In cases of serious or severe reactions, treatment should be discontinued.
- Warnings and precautions associated with the CGRP inhibitors include hypersensitivity reactions. Erenumab-aooe has additional warnings and precautions associated with the following:
  - Constipation with serious complications: Constipation with serious complications has been reported post-marketing. Some cases have required hospitalization, including surgery. Constipation was a common adverse event reported in up to 3% of patients. Concurrent use of medication associated with decreased gastrointestinal motility may increase the risk for severe constipation.
  - Hypertension: Post-marketing reports of the development or worsening of hypertension have emerged. Some cases required pharmacological treatment to manage or, in other cases, hospitalization. Incidences of hypertension were most frequently reported within 7 days of treatment, and most cases were reported after the first dose.
- The CGRP inhibitors generally have a similar incidence of adverse events as placebo. Very few severe adverse events and treatment discontinuations due to adverse events were reported. Across studies, adverse events were generally mild and/or similar to placebo. The most common adverse events observed in studies of injectable CGRP inhibitors included injection site reactions (subcutaneous CGRP inhibitors), constipation (erenumab-aooe only), and nasopharyngitis and hypersensitivity (eptinezumab-jjmr only). For the oral CGRP inhibitors, ubrogepant was associated with somnolence, and both ubrogepant and rimegepant were associated with nausea.

- There are no adequate data on the risks associated in patients who are pregnant or nursing, or in adolescent or pediatric populations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aimovig (erenumab−aooe)	Auto-injector (70 mg/mL or 140 mg/mL)	SC	Once monthly (70 or 140 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. Latex−sensitive patients may have an allergic reaction to the needle shield within the white cap and the gray needle cap of the syringe. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, erenumab-aooe has a limited stability of 7 days.
Ajovy (fremanezumab−vfrm)	Prefilled syringe (225 mg/1.5 mL)	SC	Once monthly (225 mg) or once every 3 months (675 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. The prefilled syringe cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, fremanezumab-vfrm has a limited stability of 24 hours.
Emgality (galcanezumab−gnlm)	Auto-injector (120 mg/mL) Prefilled syringe (100 mg/mL or 120 mg/mL)	SC	*Prevention of migraine*: 2 consecutive injections (120 mg each) as a loading dose, then once monthly *Episodic cluster headache*: 3 consecutive injections (100 mg each) at onset, and then once monthly until the end of the cluster period	May be self−administered by patients in the abdomen, thigh, back of upper arm or buttocks. The cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, galcanezumab-gnlm has a limited stability of 7 days.
Nurtec ODT (rimegepant sulfate)	ODT (75 mg)	PO	*Acute migraine treatment:* As needed. Maximum dose: 75 mg in 24 hours.	The safety of treating > 15 migraines in a 30-day period has not been established. Avoid concomitant administration with strong inhibitors of CYP3A4, moderate

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				or strong inducers of CYP3A, or P-gp or BCRP inhibitors.
Ubrelvy (ubrogepant)	Oral tablets (50 and 100 mg)	PO	*Acute migraine treatment:* As needed. A second dose may be taken at least 2 hours after the initial dose. Maximum dose: 200 mg in 24 hours.	The safety of treating > 8 migraines in a 30 day period has not been established. Dose adjustments are warranted with certain concomitant drugs or in cases of metabolic impairment. Avoid use in patients with end stage renal disease (CrCL < 15 mL/min). Take with or without food
Vyepti (eptinezumab-jjmr)	Single-dose vial (100 mg/mL)	IV	Once every 3 months (100 or 300 mg) The recommended dosage is 100 mg every 3 months; some patients may benefit from a dosage of 300 mg every 3 months.	Dilute with 0.9% sodium chloride injection. Following dilution, eptinezumab-jjmr must be infused within 8 hours. Infuse over approximately 30 minutes. Administered by a healthcare provider in a healthcare setting. Must be refrigerated and protected from light until time of use.

See the current prescribing information for full details
Abbreviations: CrCL = creatinine clearance; CYP = cytochrome P450; BCRP = breast cancer resistance protein; IV = intravenous; ODT = orally disintegrating tablet; P-gp = P-glycoprotein; PO = oral; SC = subcutaneous
Note: With all of the CGRP inhibitors, there are no data in pregnant women or breastfed infants. A benefit/risk assessment should be taken into consideration prior to administering.

CONCLUSION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Migraines have a spectrum of frequency and severity that can significantly affect the quality of life of patients. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period. Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women.
- Rimegepant and ubrogepant are oral CGRP inhibitors indicated for acute treatment of migraine with or without aura. The injectable CGRP inhibitors eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm are indicated for the prevention of migraine. Galcanezumab-gnlm has an additional indication for the treatment of episodic cluster headache. No CGRP inhibitor is FDA-approved for use in patients aged < 18 years. Eptinezumab-jjmr is the only IV formulation and requires administration in a healthcare setting.
- Guidelines divide treatment recommendations according to age, prevention or treatment, and migraine type:
  - Current evidence−based prophylactic migraine treatment options and guidance are limited for chronic migraine, and oral prophylactic medications prescribed for episodic migraine are often used for the preventive treatment of chronic migraine. Prophylactic migraine treatment options include oral agents (mainly anti−seizure agents, antidepressants, and beta blockers), injectable agents (onabotulinumtoxin A for chronic subtypes only), or neuromodulation devices for migraine or headache attacks. Certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. There is no optimal prophylactic migraine therapy and head-to-head trials are lacking.

- For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy according to the AHS guidelines. To date, only subcutaneous sumatriptan is FDA-approved for the acute treatment of cluster headache. Additionally, sumatriptan nasal spray, zolmitriptan oral formulations, and sphenopalatine ganglion stimulation are probably effective for acute treatment per guidelines. For prevention of cluster headaches, suboccipital steroid injections are most effective according to the guidelines; however, there is no preventive medication currently FDA-approved for cluster headache.
- For acute treatment of migraine in adults, guidelines generally recommend the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or DHE are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. Recent AHS guidelines state that rimegepant and ubrogepant may have a role in patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans.

- There are no head-to-head studies with the CGRP inhibitors and no agent is clearly superior to others. Evidence for the CGRP inhibitors have demonstrated efficacy for the respective indications:
  - Like other preventive medications for migraine, the CGRP inhibitors are not likely to render patients migraine-free. Based on 3 to 6 month data, primary endpoint reductions are similar to many oral prophylactic therapies; however, comparisons are limited as endpoints have been inconsistently defined. There are limited analyses and trials examining efficacy in patients who failed ≥ 2 prior preventive therapies; however, available data suggest that these patients may achieve greater reductions in migraine/headache frequency. Further research is warranted.
    - Compared to placebo, the CGRP inhibitors when prescribed for prophylactic migraine therapy consistently demonstrated modest but statistically significant reductions in primary endpoint measures (eg, MMD, MMH, or MMHD) ranging from 0.7 to 3.5 days after 3 to 6 months of treatment. Overall, the odds for a 50% reduction in MM(H)D were approximately 1.6 to 5.8 times higher with the CGRP inhibitors than placebo with numbers-needed to treat (NNTs) ranging from 3 to 10.
  - For the treatment of cluster headaches, galcanezumab-gnlm demonstrated efficacy compared to placebo in an 8-week trial, which allowed for acute/abortive treatments during therapy. Galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency by 3.5 during weeks 1 to 3 vs placebo. Additionally, 18.8% more patients were classified as responders (≥ 50% reduction in weekly cluster headache attack frequency) with galcanezumab-gnlm at week 3 vs placebo (p = 0.046).
  - Ubrogepant and rimegepant are oral CGRP inhibitors FDA-approved for acute treatment of migraine with or without aura in adults. One differing characteristic is that ubrogepant allows for a second dose within 24 hours whereas rimegepant does not.
    - Rimegepant ODT demonstrated efficacy compared to placebo in a Phase 3, DB, RCT which evaluated acute response to migraine treatment after 2 hours. Patients were not allowed a second dose of study treatment (placebo or rimegepant). Rescue medications allowed 2 hours post-dose included aspirin, ibuprofen, naproxen (or any other type of NSAID), APAP up to 1000 mg/day, antiemetics (eg, metoclopramide or promethazine), or baclofen. Compared to placebo, significantly more patients treated with rimegepant 75 mg were pain-free at 2 hours (difference vs placebo, 10.3%). For the co-primary endpoint of MBS, significantly more rimegepant-treated patients reported being MBS-free at 2 hours post-dose (difference vs placebo, 8.3%). Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet formulation were considered supportive for approval.
    - Ubrogepant demonstrated efficacy compared to placebo in 2 DB, RCTs, which reported acute response to migraine treatment after 2 hours. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. Compared to placebo, significantly more patients treated with ubrogepant were pain-free at 2 hours when administered the 50 mg (difference vs placebo, 7.4 to 7.5%) or 100 mg (difference vs placebo, 9.4%) dose. For the co-primary endpoint of MBS, significantly more ubrogepant-treated patients reported being MBS-free at 2 hours post dose for the 50 mg (difference vs placebo, 10.8 to 11.5%) and 100 mg (difference vs placebo, 9.9%) dose.
- Lack of information during pregnancy and breastfeeding is a consideration as many migraine patients are women of childbearing potential. The unknown risks of monoclonal antibodies and the effects on certain conditions are not fully characterized. Furthermore, rimegepant and ubrogepant have a number of drug interactions, and may not be appropriate with other medications. Important co-morbid populations were excluded from trials (eg, anxiety, depression, hypertension, and fibromyalgia), which also limits the generalizability to broader groups. There are no data in adolescents and children.

- The safety profiles of the subcutaneous CGRP inhibitors are generally mild with the most common adverse events observed being injection site reactions. Hypersensitivity and nasopharyngitis were the most commonly reported adverse events for the IV-administered agent, eptinezumab-jjmr. Mild to moderate hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, were reported with all CGRP inhibitors. Post-marketing reports with erenumab-aooe have included hypertension and constipation with serious complications; some cases of constipation have required hospitalization and surgery. The oral CGRP inhibitors, ubrogepant and rimegepant, were associated with nausea; ubrogepant was additionally associated with somnolence.
- Overall, ubrogepant and rimegepant are alternatives to triptans and/or DHE in patients who are unable to tolerate or have an inadequate response or contraindication to established pharmacologic abortive migraine treatments. The injectable CGRP inhibitors represent another therapy option in the prevention of episodic or chronic migraine. Eptinezumab-jjmr and fremanezumab-vfrm are the only agents in the class that may be administered quarterly, which may fulfill a niche in patients who are non-adherent with treatment. Galcanezumab-gnlm is the only CGRP inhibitor indicated for the treatment of episodic cluster headaches. Dosage and administration vary by product and indication. Further long-term study is warranted.

APPENDICES

- **Appendix A. AAN levels of evidence classification** *(AAN 2017, Gronseth et al 2011)*

Rating of recommendation	
A	Established as effective, ineffective, or harmful for the given condition in the specified population
B	Probably effective, ineffective, or harmful for the given condition in the specified population
C	Possibly effective, ineffective, or harmful for the given condition in the specified population
U	Data inadequate or conflicting; given current knowledge, treatment is unproven.
Rating of therapeutic article	
Class I	RCT in representative population with masked outcome assessment. The following are required: a) concealed allocation; b) primary outcome(s) is/are clearly defined; c) exclusion/inclusion criteria are clearly defined; d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias; e) certain requirements are needed for noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs.
Class II	Cohort study that meets a–e (Class I) or RCT that lacks 1 criterion from above (b−e).
Class III	Controlled trials (including well−defined natural history controls or patients serving as own controls), a description of major confounding differences between groups, and where outcome assessment is independent of patient treatment.
Class IV	Does not include patients with the disease, different interventions, undefined/unaccepted interventions or outcomes measures, and/or no measures of effectiveness or statistical precision presented or calculable.

- **Appendix B. AAN/AHS levels of evidence classification** *(Oskoui et al 2019[b])*

Level of obligation; magnitude of benefit	
A	Must; large benefit relative to harm
B	Should; moderate benefit relative to harm
C	May; small benefit relative to harm
U	No recommendation supported; too close to call

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Prior Authorization Guideline

Guideline Name Valtoco

1 . Criteria

Product Name: Valtoco (diazepam)	
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of epilepsy

AND

2 - The recipient is six years and older

AND

3 - The medication is prescribed for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern

AND

4 - ~~The prescriber documents a reason or special circumstance that precludes the use of diazepam rectal gel (Please document prescriber rationale)~~

AND

5 - The medication is prescribed by or in consultation with a neurologist

AND

6 - The quantity must not exceed five episodes per month

Product Name: Valtoco (diazepam)	
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

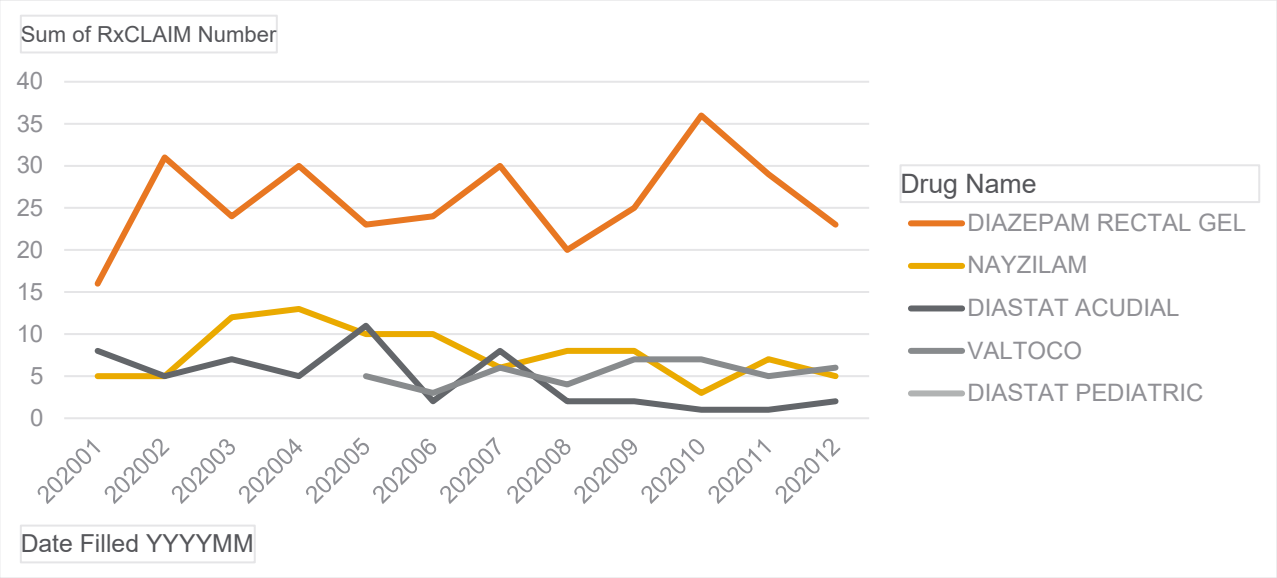
Approval Criteria

1 - Documentation of positive clinical response to Valtoco therapy

Nevada Medicaid

Benzodiazepine Anticonvulsants
Fee for Service
January 1, 2020 – December 31, 2020

Drug Name	Count of Members	Count of Claims	Total Days Supply	Total Quantity
NAYZILAM	46	92	2,116	459
DIASTAT PEDIATRIC	1	1	1	4
VALTOCO	27	43	767	292
DIASTAT ACUDIAL	27	54	1,022	135
DIAZEPAM RECTAL GEL	143	311	5,645	552



BBBB. Anticonvulsants

Therapeutic Class: Anticonvulsants
Last Reviewed by the DUR Board: July 23, 2020

Anticonvulsants are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Cannabinoid

   a. Epidiolex® (cannabidiol)

      1. Approval will be given if the following criteria are met and documented:

         a. The recipient has a diagnosis of Lennox-Gastaut syndrome or Dravet Syndrome; and

         b. The recipient is two years of age or older; and

         c. A recent serum transaminase (ALT and AST) and total bilirubin level has been obtained and is within normal limits; and

         d. The drug is prescribed by or in consultation with a neurologist; and

         e. The total dose does not exceed 20 mg/kg/day (10mg/kg twice daily); and

         f. The medication will be used as adjunctive therapy (the recipient has been taking one or more antiepileptic drugs and has chart notes confirming the presence of at least four convulsive seizures per month).

      2. Recertification Request:

         a. Documentation of a positive clinical response to Epidiolex® therapy; and

         b. Serum transaminase (ALT and AST) and total bilirubin level has been re-checked per package insert.

      3. Prior Authorization Guidelines:

         a. Initial prior authorization will be for three months.

         b. Recertification approval will be for 12 months.

         c. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

4. For anticonvulsant criteria for children and adolescents, refer to Section N, titled Psychotropic Medications for Children and Adolescents.

2. Nayzilam® (midazolam)

a. Approval will be given if the following criteria are met and documented:

1. The recipient has a diagnosis of acute intermittent seizures; and

2. The recipient is at least 12 years of age; and

3. The medication is prescribed by or in consultation with a Neurologist; and

4. The dose must not exceed two sprays per seizure cluster, no more than one episode every three days and treat no more than five episodes per month.

b. Recertification Request:

1. Documentation of positive clinical response to Nayzilam® therapy.

c. Prior Authorization Guidelines:

1. Initial prior authorization will be for six months.

2. Recertification approval will be for 12 months.

3. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

3. Valtoco® (diazepam)

a. Approval will be given if all the following criteria are met and documented:

1. The recipient has a diagnosis of epilepsy; and

2. The recipient is six years and older; and

3. The medication is prescribed for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern; and

4. The prescriber documents a reason or special circumstance that precludes the use of diazepam rectal gel; and

5. The medication is prescribed by or in consultation with a neurologist; and

6. The quantity must not exceed five episodes per month.

b. Prior Authorization Guidelines:

1. Documentation of positive clinical response to Valtoco® theraphy.

c. Prior Authorization Guidelines:

1. Initial authozition will be approved for six months.

2. Recertification approval will be approved for 12 months.

3. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

Therapeutic Class Overview
Anticonvulsants

INTRODUCTION

- Epilepsy is a disease of the brain defined by any of the following (*Fisher et al 2014*):
  - At least 2 unprovoked (or reflex) seizures occurring > 24 hours apart;
  - 1 unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years;
  - Diagnosis of an epilepsy syndrome.
- Types of seizures include generalized seizures, focal (partial) seizures, and status epilepticus (*Centers for Disease Control and Prevention [CDC] 2018, Epilepsy Foundation Greater Chicago 2020*).
  - Generalized seizures affect both sides of the brain and include:
    - Tonic-clonic (grand mal): begin with stiffening of the limbs, followed by jerking of the limbs and face
    - Myoclonic: characterized by rapid, brief contractions of body muscles, usually on both sides of the body at the same time
    - Atonic: characterized by abrupt loss of muscle tone; they are also called drop attacks or akinetic seizures and can result in injury due to falls
    - Absence (petit mal): characterized by brief lapses of awareness, sometimes with staring, that begin and end abruptly; they are more common in children than adults and may be accompanied by brief myoclonic jerking of the eyelids or facial muscles, a loss of muscle tone, or automatisms.
  - Focal seizures are located in just 1 area of the brain and include:
    - Simple: affect a small part of the brain; can affect movement, sensations, and emotion, without a loss of consciousness
    - Complex: affect a larger area of the brain than simple focal seizures and the patient loses awareness; episodes typically begin with a blank stare, followed by chewing movements, picking at or fumbling with clothing, mumbling, and performing repeated unorganized movements or wandering; they may also be called “temporal lobe epilepsy” or “psychomotor epilepsy”
    - Secondarily generalized seizures: begin in 1 part of the brain and spread to both sides
  - Status epilepticus is characterized by prolonged, uninterrupted seizure activity.
- Seizure classifications from the International League against Epilepsy (ILAE) were updated in 2017. The ILAE classification of seizure types is based on whether the seizure has a focal, generalized, or unknown onset; has a motor or non-motor onset; and whether the patient is aware or has impaired awareness during the event (for focal seizures). Additional classification details may also be used (*Fisher et al 2017A, Fisher et al 2017B*).
  - There is variation between the ILAE classifications and many of the Food and Drug Administration (FDA)-approved indications for antiepileptic drugs (AEDs). For example, a “focal aware” seizure corresponds to the prior term “simple partial seizure,” and a “focal impaired awareness” seizure corresponds to the prior term “complex partial seizure.”
- A number of epilepsy syndromes have also been described; these are defined by groups of features that tend to occur together such as having a similar seizure type, age of onset, part of the brain involved, and electroencephalogram (EEG) pattern (*Epilepsy Foundation 2013*). An example is a childhood epilepsy syndrome called Lennox-Gastaut syndrome (LGS), which is characterized by several seizure types including tonic (stiffening) and atonic (drop) seizures. In LGS, there is a classic EEG pattern seen and intellectual development is usually impaired (*Epilepsy Foundation 2020*).
- Epilepsy management is focused on the goals of 1) controlling seizures, 2) avoiding treatment-related adverse effects (AEs), and 3) maintaining or restoring quality of life. Management options vary based on the seizure type. It is usually appropriate to refer patients to a neurologist to establish the epilepsy diagnosis and formulate the management strategy (*Schachter 2019*).
  - A correct diagnosis is essential to proper treatment selection. For example, absence seizures are commonly confused with complex partial seizures. However, drugs that reduce absence seizures are generally ineffective for complex partial seizures, and the most effective drugs for complex partial seizures may be ineffective against or even increase the frequency of absence seizures (*Epilepsy Foundation Greater Chicago 2020*).

- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. When combination therapy is needed, it is recommended to select products with different mechanisms of action and AE profiles. There is little comparative clinical data to support the use of specific combinations (*Schachter 2019*).
- Several broad classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents (see Table 1).
- Cannabidiol (Epidiolex) was FDA-approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It was the first FDA-approved drug for treatment of patients with Dravet syndrome and the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. In July 2020, cannabidiol was FDA-approved for the treatment of seizures associated with tuberous sclerosis complex (TSC) in pediatric patients 1 year of age and older (*Epidiolex prescribing information 2020, FDA news release 2020)*. The age range for the indications of treatment of seizures associated with LGS or Dravet syndrome was also expanded to include pediatric patients 1 year of age and older (*Epidiolex prescribing information 2020)*. Initially designated as a schedule V controlled substance, cannabidiol has been descheduled and is no longer classified as a controlled substance.
- Stiripentol (Diacomit) capsules and powder for oral suspension were FDA-approved in August 2018 for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam. In June 2020, fenfluramine oral solution (Fintepla) was approved for the same indication without the requirement for concomitant clobazam (*Fintepla prescribing information 2020*).
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication in April 2018 for use in partial-onset seizures associated with TSC. This product is a kinase inhibitor that also has several oncology indications.
- Midazolam nasal spray (Nayzilam) was approved in May 2019 for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age (*Nayzilam prescribing information 2019*). In January 2020, diazepam nasal spray (Valtoco) was approved for the same indication in patients as young as 6 years of age (*Valtoco prescribing information 2020*).
- Several of the AEDs are used for additional indications beyond the management of epilepsy, including (but not limited to) bipolar disorder, migraine prophylaxis, and several types of neuropathic pain. These additional indications are listed in Table 2; however, this review primarily focuses on the use of AEDs for the management of epilepsy. Additionally, brands and formulations FDA-approved and marketed only for non-epilepsy indications are not included within this review; these include gabapentin tablets (Gralise), FDA-approved only for the management of postherpetic neuralgia, gabapentin enacarbil extended-release tablets (Horizant), FDA-approved only for management of postherpetic neuralgia and treatment of moderate-to-severe restless leg syndrome, and pregabalin extended-release tablets (Lyrica CR), FDA-approved only for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.
- Medispan class: Antianxiety agents, benzodiazepines; Anticonvulsants, AMPA glutamate receptor antagonists; Anticonvulsants, anticonvulsants – misc; Anticonvulsants, carbamates; Anticonvulsants, GABA modulators; Anticonvulsants, hydantoins; Anticonvulsants, succinimides; Anticonvulsants, valproic acid; Hypnotics/Sedatives/Sleep Disorder Agents, barbiturate hypnotics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Barbiturates	
Pentobarbital (Nembutal)	✔
Phenobarbital* (Luminal†, Solfoton†)	✔
Primidone (Mysoline)	✔
Benzodiazepines	
Clobazam (Onfi; Sympazan)	✔ ***
Clonazepam (Klonopin§)	✔
Clorazepate (Tranxene T-Tab§)	✔
Diazepam (Diastat¶, Valium,§ Valtoco)	✔ ‖
Midazolam (Nayzilam)	-
Hydantoins	
Ethotoin (Peganone)	-

Drug	Generic Availability
Fosphenytoin (Cerebyx)	✔
Phenytoin (Dilantin§, Phenytek)	✔ ‖
Miscellaneous	
Brivaracetam (Briviact)	-
Cenobamate (Xcopri)	-
Cannabidiol (Epidiolex)	-
Carbamazepine (Carbatrol, Epitol**, Equetro, Tegretol§, Tegretol-XR)	✔
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	✔
Eslicarbazepine (Aptiom)	-
Ethosuximide (Zarontin)	✔
Everolimus (Afinitor Disperz)	-
Felbamate (Felbatol)	✔
Fenfluramine (Fintepla)	-
Gabapentin (Neurontin)	✔
Lacosamide (Vimpat)	-
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite**)	✔
Levetiracetam (Keppra, Keppra XR, Roweepra**, Roweepra XR**, Spritam, Elepsia XR)	✔ ‖
Methsuximide (Celontin)	-
Oxcarbazepine (Oxtellar XR, Trileptal)	✔ ‖
Perampanel (Fycompa)	-
Pregabalin (Lyrica)	✔
Rufinamide (Banzel)	- ¶¶
Stiripentol (Diacomit)	-
Tiagabine (Gabitril)	✔
Topiramate (Topamax, Topamax Sprinkle, Topiragen††, Trokendi XR, Qudexy XR¶)	✔ ‖
Valproic acid/valproate sodium (Depacon†, Depakene†)	✔
Vigabatrin (Sabril, Vigadrone**)	✔ ‖
Zonisamide (Zonegran§)	✔

* Not FDA approved
† Brand product not currently marketed; generic is available
§ Brand marketing status may vary by strength and/or formulation
‖ Generic availability may vary by strength and/or formulation
¶ Authorized generic available; no A-rated generics approved via abbreviated new drug application
** Branded generic
†† Branded generic; not currently marketed
***Generic available for Onfi tablets and oral suspension; only brand name available for Sympazan oral film
¶¶ Generic product has been FDA-approved, but not currently marketed

(*Clinical Pharmacology 2020, Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

- Tables 2A and 2B provide an overview of anticonvulsant indications. Except where noted, only FDA-approved products and indications are included. For items marked with an asterisk, there is additional information about the indication provided in the box following the tables.
- Acute-care indications that are not related to convulsive disorders (for example, pre-procedural use of benzodiazepines in hospital settings) are not included.

Table 2A. Indications for anticonvulsants (Part 1 of 2)

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Cenobamate	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Felbamate	Fenfluramine	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Partial seizures (simple partial, complex partial and/or secondarily generalized)	✔ *		✔ *	✔ *			A		✔, A*	✔, A*		✔ *		✔, A*			A*	✔ *	✔, A*	✔ *
Primary generalized tonic-clonic seizure (grand mal)			✔									✔				✔ *			A*	A*
Absence seizure (petit mal)						✔ *			✔, A*		✔									
Multiple seizure types that include absence seizures									A											
Seizures of Lennox-Gastaut syndrome (LGS)		✔ *			A*	✔, A								A*					A*	
Seizures of Dravet syndrome		✔ *													✔ *					
Juvenile myoclonic epilepsy (JME)																				A*
Emergency/acute/short-term use for seizure control (see notes)								✔ *								✔ *				
Akinetic and myoclonic seizures						✔, A														
Convulsive disorders (see notes)								A*												
Certain mixed seizure patterns or other partial or generalized seizures			✔ *																	
Migraine prophylaxis									✔ *											
Trigeminal neuralgia			✔ *																	
Postherpetic neuralgia																	✔ *			
Bipolar disorder			✔ *						✔ *										✔ *	
Panic disorder, with or without agoraphobia						✔														
Anxiety disorder; short-term relief of anxiety symptoms							✔	✔												
Symptomatic relief of acute alcohol withdrawal							✔	✔												

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Cenobamate	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Felbamate	Fenfluramine	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Relief of skeletal muscle spasm, spasticity, athetosis, and stiff-man syndrome								A												
Seizures associated with tuberous sclerosis complex (TSC)		✓ *											A*							

✓ = monotherapy (or not specified); A = adjunctive therapy

Table 2B. Indications for Anticonvulsants (Part 2 of 2)

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Partial seizures (simple partial, complex partial and/or secondarily generalized)			✓, A*		✓ *		✓ *	A*	✓, A*			A*	✓, A*	✓, A*	A*	A*
Primary generalized tonic-clonic seizure (grand mal)					A*		✓ *		✓, A*				✓, A*			
Absence seizure (petit mal)		✓ *												✓, A*		
Multiple seizure types which include absence seizures														A*		
Seizures of LGS										A*			A*			
Seizures of Dravet syndrome											A*					
Emergency/acute/ short-term use for seizure control (see notes)	✓ *			✓ *			✓ *									
Infantile spasms															✓ *	
Convulsive disorders (see notes)						✓ *										
Migraine prophylaxis													✓ *	✓ *		
Postherpetic neuralgia								✓								
Bipolar disorder														✓ *		

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Sedative for anxiety, tension, and apprehension																
Neuropathic pain associated with diabetic peripheral neuropathy								✔								
Neuropathic pain associated with spinal cord injury								✔								
Fibromyalgia								✔								

✓ = monotherapy (or not specified); A = adjunctive therapy
†Phenobarbital is not approved by the FDA.

***Notes: Additional Detail on Selected Anticonvulsant Indications**

- Brivaracetam:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (oral formulations); ≥ 16 years of age (IV formulation)
- Cannabidiol:
  - Treatment of seizures associated with LGS, Dravet syndrome, or TSC in patients ≥ 1 year of age
- Carbamazepine:
  - Partial seizures with complex symptomatology (psychomotor, temporal lobe); patients with these seizures appear to show greater improvement than those with other types; generalized tonic-clonic seizures (grand mal); mixed seizure patterns which include the above, or other partial or generalized seizures
  - Absence seizures (petit mal) do not appear to be controlled; carbamazepine has been associated with increased frequency of generalized convulsions in these patients
  - Treatment of pain associated with true trigeminal neuralgia; beneficial results also reported in glossopharyngeal neuralgia
  - Bipolar indication is for an extended-release capsule formulation (Equetro) only: treatment of patients with acute manic or mixed episodes associated with bipolar I disorder
- Cenobamate:
  - Partial-onset seizures in adult patients
- Clobazam:
  - Seizures associated with LGS in patients ≥ 2 years of age
- Clonazepam:
  - In patients with absence seizures who have failed to respond to succinimides, clonazepam may be useful
- Diazepam:
  - Oral diazepam may be used adjunctively in convulsive disorders; it has not proved useful as sole therapy.
  - Rectal diazepam is indicated in the management of selected, refractory patients with epilepsy on stable regimens of AEDs who require intermittent use of diazepam to control bouts of increased seizure activity
  - Injectable diazepam is a useful adjunct in status epilepticus and severe recurrent convulsive seizures
  - Diazepam nasal spray is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 6 years of age
- Divalproex sodium:

- Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures (≥ 10 years of age for all formulations)
- Monotherapy and adjunctive therapy in the treatment of simple and complex absence seizures (≥ 10 years of age for extended-release tablets; age not specified for tablets/sprinkle capsules)
- The tablets and extended-release tablets have indications in bipolar disorder and migraine prophylaxis; the sprinkle capsule formulation does not. For bipolar disorder, safety and effectiveness for long-term use (> 3 weeks) has not been demonstrated in controlled clinical trials. Bipolar disorder indications are as follows:
  - Treatment of the manic episodes associated with bipolar disorder (tablets)
  - Treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features (extended-release tablets)

- Eslicarbazepine:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age
- Ethotoin:
  - Complex partial (psychomotor) seizures
- Everolimus:
  - Adjunctive treatment of adult and pediatric patients ≥ 2 years of age with TSC-associated partial-onset seizures (tablets for oral suspension only)
- Felbamate:
  - Not first-line; recommended only in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or renal failure is deemed acceptable
  - Monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy
  - Adjunctive therapy of partial and generalized seizures associated with LGS in children (age not specified)
- Fenfluramine:
  - Treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age
- Fosphenytoin:
  - Treatment of generalized tonic-clonic status epilepticus
  - Prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted short-term for oral phenytoin when oral phenytoin administration is not possible
- Gabapentin:
  - Adjunctive therapy in the treatment of partial-onset seizures, with and without secondary generalization, in adults and pediatric patients ≥ 3 years of age with epilepsy.
  - Management of postherpetic neuralgia in adults
- Lacosamide:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (tablet and oral solution)
  - Treatment of partial-onset seizures in patients ≥ 17 years of age (injection)
- Lamotrigine immediate-release formulations:
  - Age ≥ 2 years for adjunctive therapy for partial-onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of LGS
  - Age ≥ 16 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED
  - Maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (treatment of acute manic or mixed episodes is not recommended)
- Lamotrigine extended-release tablets:
  - Age ≥ 13 years for adjunctive therapy for primary generalized tonic-clonic seizures and partial-onset seizures with or without secondary generalization, and age ≥13 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with a single AED
  - The extended-release formulation is not FDA-approved for bipolar disorder
- Levetiracetam:
  - Tablets, oral solution, injection, and tablets for oral suspension:
    - Treatment of partial-onset seizures in patients ≥ 1 month of age (tablets, oral solution, and injection [Keppra]); adjunctive treatment for partial-onset seizures in patients ≥ 4 years of age and weighing > 20 kg (tablets for oral suspension [Spritam])

        - Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents ≥ 12 years of age with JME
        - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children ≥ 6 years of age with idiopathic generalized epilepsy
    - The extended-release tablets are only indicated for the treatment of partial-onset seizures in patients ≥ 12 years of age
- Methsuximide:
    - Control of absence (petit mal) seizures that are refractory to other drugs
- Midazolam nasal spray:
    - Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age.
- Oxcarbazepine immediate-release formulations:
    - Monotherapy in the treatment of partial seizures in adults and children 4 to 16 years of age
    - Adjunctive therapy in the treatment of partial seizures in adults and children 2 to 16 years of age
- Oxcarbazepine extended-release tablets:
    - Treatment of partial-onset seizures in adults and children ≥ 6 years of age
- Pentobarbital:
    - In anesthetic doses in the emergency control of certain acute convulsive episodes, eg, those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics
- Perampanel:
    - Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy ≥ 4 years of age
    - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with epilepsy ≥ 12 years of age
- Phenobarbital (not FDA-approved):
    - Phenobarbital tablets are indicated for use as an anticonvulsant; the elixir is indicated for the treatment of generalized and partial seizures; the injection is indicated as an anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures, in the emergency control of certain acute convulsive episodes, and in pediatric patients as an anticonvulsant
- Phenytoin oral formulations:
    - Treatment of tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery (the oral suspension does not have the neurosurgery indication)
- Phenytoin injection:
    - Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery
    - Can be substituted as short-term use for oral phenytoin when oral phenytoin administration is not possible
- Pregabalin:
    - Adjunctive therapy for treatment of partial-onset seizures in patients ≥ 1 month of age
- Primidone:
    - Control of grand mal, psychomotor, and focal epileptic seizures; may control grand mal seizures refractory to other anticonvulsant therapy
- Rufinamide:
    - Adults and pediatric patients ≥ 1 year of age
- Stiripentol:
    - Treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age taking clobazam; no clinical data to support its use as monotherapy
- Tiagabine:
    - Adjunctive therapy in adults and children ≥ 12 years of age in the treatment of partial seizures
- Topiramate:

- Initial monotherapy in patients with partial-onset or primary generalized tonic-clonic seizures (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
- Adjunctive therapy for adults and pediatric patients with partial-onset seizures or primary generalized tonic-clonic seizures and in patients with seizures associated with LGS (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
- Prophylaxis of migraine headache in patients ≥ 12 years of age

- Valproic acid/valproate sodium:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures; sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures
- Vigabatrin:
  - Adjunctive therapy for patients ≥ 2 years of age with refractory complex partial seizures who have responded inadequately to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss
  - Monotherapy for patients with infantile spasms 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss
- Zonisamide:
  - Adjunctive therapy in the treatment of partial seizures in adults with epilepsy

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. Clinical trial data demonstrating efficacy of the anticonvulsants for the treatment of epilepsy is described in the prescribing information for the individual products, particularly for anticonvulsants more recently approved by the FDA. However, the prescribing information for some older, conventional products (eg, benzodiazepines, carbamazepine, ethotoin, ethosuximide, methsuximide, phenytoin, and primidone) and non-FDA approved products (eg, phenobarbital) do not contain efficacy data in their prescribing information.
- No single AED is clearly the most effective. Comparative efficacy data for the management of epilepsy are limited, and trials have generally not shown significant differences among drugs in terms of efficacy. However, the quality of the data is limited and generally derived from short-term trials (*Karceski 2019*).
- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. (*Schachter 2019*). Most patients with epilepsy are treated with anticonvulsant monotherapy (*Nevitt et al 2017*).
- An evidence review summarized AED efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes (*Glauser et al 2013*). This publication provides conclusions based on a review of 64 randomized trials and 11 meta-analyses. Conclusions include the following:
  - As initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures:
    - Carbamazepine, levetiracetam, phenytoin, and zonisamide are established as efficacious/effective.
    - Valproate is probably efficacious/effective.
    - Gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin are possibly efficacious/effective.
    - Clonazepam and primidone are potentially efficacious/effective.
  - As initial monotherapy for children with newly diagnosed or untreated partial-onset seizures:
    - Oxcarbazepine is established as efficacious/effective.
    - Carbamazepine, phenobarbital, phenytoin, topiramate, valproate, and vigabatrin are possibly efficacious/effective.
    - Clobazam, carbamazepine, lamotrigine, and zonisamide are potentially efficacious/effective.
  - As initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures:
    - Gabapentin and lamotrigine are established as efficacious/effective.
    - Carbamazepine is possibly efficacious/effective.
    - Topiramate and valproate are potentially efficacious/effective.

- As initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
  - Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
  - Gabapentin, levetiracetam, and vigabatrin are potentially efficacious/effective.
  - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
- For children with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
  - Carbamazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
  - Oxcarbazepine is potentially efficacious/effective.
  - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
- As initial monotherapy for children with newly diagnosed or untreated absence seizures:
  - Ethosuximide and valproate are established as efficacious/effective.
  - Lamotrigine is possibly efficacious/effective.
  - Gabapentin is established as inefficacious/ineffective.
  - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence seizures (based on scattered reports).
- As initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes (BECTS):
  - Carbamazepine and valproate are possibly efficacious/effective.
  - Gabapentin, levetiracetam, oxcarbazepine, and sulthiame (not available in the United States) are potentially efficacious/effective.
- For patients with newly diagnosed JME:
  - Topiramate and valproate are potentially efficacious/effective.
  - Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence, myoclonic, and in some cases generalized tonic-clonic seizures. There has also been a report that lamotrigine may exacerbate seizures in JME.
- There is a lack of well-designed randomized trials in epilepsy, particularly for generalized seizures and in the pediatric population.

- A Cochrane systematic review evaluated the efficacy of AED monotherapy for epilepsy (*Nevitt et al 2017*). The review included the use of carbamazepine, phenytoin, valproate, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, and zonisamide for the treatment of partial-onset seizures (simple partial, complex partial or secondarily generalized) or generalized tonic-clonic seizures with or without other generalized seizure types.
  - This network meta-analysis showed that for the primary outcome, the time to withdrawal of allocated treatment:
    - For individuals with partial seizures, levetiracetam performed better than carbamazepine and lamotrigine; lamotrigine performed better than all other treatments (aside from levetiracetam); and carbamazepine performed better than gabapentin and phenobarbital.
    - For individuals with generalized onset seizures, valproate performed better than carbamazepine, topiramate and phenobarbital.
    - For both partial and generalized onset seizures, phenobarbital seems to perform worse than all other treatments.
  - For the secondary outcome, time to first seizure:
    - For individuals with partial seizures, phenobarbital performed better than both carbamazepine and lamotrigine; carbamazepine performed better than valproate, gabapentin, and lamotrigine; and phenytoin performed better than lamotrigine.
    - For both partial and generalized seizure types, phenytoin and phenobarbital generally performed better than other treatments.
  - Few notable differences were shown for either partial or generalized seizure types for the secondary outcomes of time to 6-month or 12-month remission of seizures.
  - Overall, direct evidence and network meta-analysis estimates were numerically similar, and effect sizes had overlapping confidence intervals.
  - Data for individuals with generalized seizures are still limited and additional randomized trials are needed.
- The relative efficacy among valproate, lamotrigine, phenytoin, carbamazepine, ethosuximide, topiramate, levetiracetam, and phenobarbital as monotherapy for generalized (n = 7 studies) or absence seizures (n = 3 studies) was evaluated in a systematic review and network meta-analysis (*Campos et al 2018*). The outcomes analyzed were seizure freedom and withdrawal due to inefficacy. Compared to valproate, phenytoin had a lower odds of seizure freedom (odds ratio, 0.50;

95% credible Interval [CrI] 0.27 to 0.87) in patients with generalized tonic-clonic seizures. Lamotrigine had the highest probability of seizure freedom and valproate had the highest probability of withdrawal due to inefficacy in these patients. For absence seizures, ethosuximide and valproate were found to have a higher probability of seizure freedom compared to lamotrigine.

- A meta-analysis estimated the comparative efficacy of achieving seizure freedom with 22 antiepileptic drugs and placebo in children and adolescents (*Rosati et al 2018*). For the treatment of newly diagnosed focal epilepsy (n = 4 studies), point estimates suggested superiority of carbamazepine and lamotrigine; however, this was not statistically significant. For refractory focal epilepsy (n = 9 studies), levetiracetam and perampanel were more effective than placebo in mixed comparisons. Ethosuximide and valproic acid were more effective than lamotrigine for absence seizures. The authors concluded that better designed comparative studies with appropriate length of follow-up, well-defined outcomes, and reliable inclusion criteria are needed to validate these results.
- A meta-analysis compared monotherapy with carbamazepine or phenytoin in children and adults with focal onset seizures (simple or complex focal and secondarily generalized), or generalized onset tonic-clonic seizures (with or without other generalized seizure types). Results demonstrated that the time to treatment failure (primary outcome) did not significantly differ between treatment groups. The time to first seizure after randomization and 6-month and 12-month remission were also similar between groups (*Nevitt et al 2019).*
- Approximately 20% to 40% of patients with epilepsy can be considered refractory to drug treatment, referred to as drug-resistant epilepsy. Treatment of drug-resistant epilepsy may include additional anticonvulsant drug trials, epilepsy surgery, vagal nerve stimulation, and dietary changes (the ketogenic diet) (*Sirven 2018*).
  - Combination AED regimens are an option for the treatment of drug-resistant epilepsy. However, robust clinical evidence of suitable combinations of AEDs has been difficult to generate due to the large number of possible combinations of drugs and doses. Examples of combinations for which there is some evidence of efficacy include valproate plus lamotrigine for partial-onset and generalized seizures, valproate plus ethosuximide for absence seizures, and lamotrigine plus topiramate for various seizure types; however, even this evidence is fairly limited. In general, when considering combination therapy, it is recommended to combine medications with different mechanisms of action, and to be mindful of the overall drug load to minimize AEs. Two-drug therapy should be attempted before considering addition of a third drug, and higher numbers of drugs should be avoided as they are associated with a very low likelihood of additional seizure reduction (*Kwan et al 2011*).
  - A meta-analysis examined the efficacy of newer AEDs (eslicarbazepine, brivaracetam, perampanel, and lacosamide) vs levetiracetam as adjunctive therapy for uncontrolled partial-onset seizures. Most patients in this meta-analysis were on at least 2 other AEDs at the time of treatment. In this analysis, eslicarbazepine, lacosamide, and brivaracetam were non-inferior to levetiracetam in terms of efficacy, but all newer AEDs except brivaracetam had worse tolerability profiles than levetiracetam at high doses (*Zhu et al 2017*).
  - A network meta-analysis examined the efficacy of AEDs (including brivaracetam, eslicarbazepine acetate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, pregabalin, perampanel, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide) for adjunctive use in patients with refractory partial-onset seizures while using monotherapy (*Zhao et al 2017*). The efficacy outcomes studied were 50% responder rate and state of seizure freedom. The authors concluded that topiramate, levetiracetam, pregabalin, and oxcarbazepine were preferable for their relatively high efficacy and low risk of AEs. Rufinamide was the least preferable medication due to its low efficacy and high risk of AEs.
  - A network meta-analysis was conducted to evaluate the efficacy of 17 newer AEDs for treatment of refractory partial-onset epilepsy with or without secondary generalization (*Hu et al 2018*). The primary outcome was seizure freedom, which was defined as a 100% seizure reduction in the maintenance or double-blind treatment period of the trial. Safety was assessed by the withdrawal rate due to treatment-emergent AEs. Based on results of 54 studies that evaluated the efficacy outcome, the most effective agents included tiagabine, brivaracetam, and valproic acid, and the least effective agents included rufinamide, lamotrigine, and zonisamide. Products with favorable safety included levetiracetam, brivaracetam, and perampanel, while those with the least favorable safety included retigabine (not available in the United States), oxcarbazepine, and rufinamide. The authors stated that agents with the best outcomes in terms of efficacy and safety included levetiracetam, vigabatrin, valproic acid, and brivaracetam.
  - Cannabidiol (Epidiolex) was approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Its approval for these 2 indications was based on 3 placebo-controlled trials in patients refractory to other treatments.

Cannabidiol, along with use of other agents, demonstrated a significant reduction in seizure frequency compared to placebo (*Thiele et al 2018*; *Devinsky et al 2018; Devinsky et al 2017*). In July 2020, cannabidiol was FDA-approved for a third indication, treatment of seizures associated with TSC, and the age range for all 3 indications was aligned to include pediatric patients 1 year of age and older (*FDA news release 2020, Epidiolex prescribing information 2020)*. In a placebo-controlled trial of 224 patients with TSC and seizures inadequately controlled with ≥ 1 concomitant AED, cannabidiol resulted in a significant reduction in seizure frequency compared to placebo (*Epidiolex prescribing information 2020*). To date, no comparative trials have been published.

- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication for adjunctive use in TSC-associated partial-onset seizures in April 2018. Results of a randomized, double-blind, placebo-controlled study of 366 patients with inadequately controlled seizures on 2 or more AEDs demonstrated a significant reduction in seizure frequency compared to placebo (*French et al 2016*).
- In August 2018, the FDA approved a second drug, stiripentol (Diacomit), for use in the treatment of seizures associated with Dravet syndrome. Two multicenter placebo-controlled studies evaluated the addition of stiripentol to clobazam and valproate therapy in patients 3 years to less than 18 years of age with Dravet syndrome. Responder rates (seizure frequency reduced by 50%) with respect to generalized tonic-clonic seizures were significantly lower with stiripentol compared to placebo (*Diacomit prescribing information 2018).*
- In May 2019, a nasal spray formulation of midazolam (Nayzilam) was approved for the acute treatment of cluster seizures in adults and adolescents. In one randomized controlled trial in patients with seizure clusters while receiving a stable AED regimen, the proportion of patients who experienced treatment success (seizure termination within 10 minutes and no recurrence for the next 6 hours) was significantly higher with midazolam nasal spray compared to placebo (53.7% vs 34.4%, p = 0.0109) with similar tolerability (*Detyniecki et al 2019*).
- Cenobamate was approved in late 2019 and its efficacy has yet to be compared to other AEDs. The approval of this agent was based on 2 multicenter, randomized, double-blind, placebo-controlled studies that enrolled 655 adults with partial-onset seizures with or without generalization who were not adequately controlled with 1 to 3 other AEDs. The results of these trials demonstrated that cenobamate significantly reduced the frequency of seizures occurring in a 28-day period. In the first trial, the median percent change in seizure frequency from baseline was -55.6% with cenobamate and -21.5% with placebo. In the second trial, the median percent change ranged from -36.3% to -55.3% with cenobamate and was -24.3% with placebo (*Xcopri package insert 2019, Krauss et al 2020*).
- In June 2020, the FDA approved a third drug, fenfluramine (Fintepla), for use in the treatment of seizures associated with Dravet syndrome. Two randomized, double-blind, placebo-controlled studies evaluated fenfluramine in patients 2 to 18 years of age with Dravet syndrome who were inadequately controlled with 1 to 4 other AEDs. In both trials, fenfluramine significantly reduced the frequency of convulsive seizures occurring in a 28-day period as compared to placebo. In the first trial, in patients not receiving stiripentol, fenfluramine at a dose of 0.7 mg/kg/day demonstrated a 62.3% greater reduction in mean monthly convulsive seizure frequency (MCSF) over 14 weeks compared with placebo. In the second trial, in patients who were receiving a stiripentol-inclusive AED regimen, fenfluramine at a dose of 0.4 mg/kg/day showed a 54% greater reduction in MCSF over 15 weeks compared with placebo (*Fintepla package insert 2020, Lagae et al 2020, Nabbout et al 2019*).
- A 2019 randomized controlled trial of children and adults with benzodiazepine-refractory convulsive status epilepticus compared the efficacy of intravenous levetiracetam (n = 145 patients), fosphenytoin (n = 118), or valproate (n = 121) in this setting. Results demonstrated that each agent led to seizure cessation and improved alertness by 1 hour in approximately 50% of patients, with no significant differences between groups (*Kapur et al 2019*).
- A meta-analysis of 9 randomized controlled trials evaluated the efficacy and safety of levetiracetam vs phenytoin as second-line treatment for benzodiazepine-resistant status epilepticus in children and adults. The efficacy outcomes included seizure cessation and seizure recurrence within 24 hours. The authors did not find a significant difference in efficacy between levetiracetam and phenytoin in the overall population or in the subgroup analysis of pediatric patients. AEs were similar across both groups except for a higher incidence of cardiac instability, reported mainly as hypotension, in the phenytoin group (*DeMott et al 2020).*

CLINICAL GUIDELINES

- **Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy**. American Academy of Neurology and American Epilepsy Society (*French et al 2004A, Kanner et al, 2018A*).
  - A 2018 update to the 2004 guideline focuses on treatment of new-onset epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate,

tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with newly diagnosed partial and generalized epilepsies.
  - The recommendations from the 2004 guideline include the following:
    - Patients with newly diagnosed epilepsy who require treatment can be initially treated with standard AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital, or on the newer AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice will depend on individual patient characteristics.
    - Lamotrigine can be included in the options for children with newly diagnosed absence seizures.
  - The 2018 recommendations include the following:
    - As monotherapy in adult patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures:
      - Lamotrigine use should be considered to decrease seizure frequency.
      - Lamotrigine use should be considered and gabapentin use may be considered to decrease seizure frequency in patients aged ≥ 60 years.
      - Levetiracetam and zonisamide use may be considered to decrease seizure frequency.
      - Vigabatrin appears to be less efficacious than carbamazepine immediate-release and may not be offered; furthermore, the toxicity profile precludes vigabatrin use as first-line therapy.
      - Pregabalin 150 mg per day is possibly less efficacious than lamotrigine 100 mg per day.
      - There is insufficient evidence to consider use of gabapentin, oxcarbazepine, or topiramate over carbamazepine.
      - There is insufficient evidence to consider use of topiramate instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic seizures, or generalized epilepsy presenting with generalized tonic-clonic seizures.
      - Data are lacking to support or refute use of third-generation AEDs (eslicarbazepine, ezogabine [no longer marketed], lacosamide, perampanel, pregabalin, and rufinamide), clobazam, felbamate, or vigabatrin for new-onset epilepsy.
      - Data are lacking to support or refute use of newer AEDs in treating unclassified generalized tonic-clonic seizures.
    - Ethosuximide or valproic acid should be considered before lamotrigine to decrease seizure frequency in children with absence epilepsy. An exception would be if there are compelling AE-related concerns with use of ethosuximide or valproic acid.
    - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.
- **Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy**. American Academy of Neurology and American Epilepsy Society (*Kanner et al 2018B*, *French et al 2004B*).
  - A 2018 update to the 2004 guideline focuses on management of treatment-resistant epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with refractory partial and generalized epilepsies.
  - Recommendations from the 2004 guideline include the following:
    - It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide as add-on therapy in patients with refractory epilepsy.
    - Oxcarbazepine, topiramate, and lamotrigine can be used as monotherapy in patients with refractory partial epilepsy.
    - Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children.
    - Gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of children with refractory partial seizures.
    - Topiramate and lamotrigine may be used to treat drop attacks associated with LGS in adults and children.
  - Recommendations from the 2018 guideline include the following:
    - As adjunctive therapy in patients with treatment-resistant adult focal epilepsy (TRAFE):
      - Immediate-release pregabalin and perampanel are established as effective to reduce seizure frequency.
      - Lacosamide, eslicarbazepine, and extended-release topiramate should be considered to decrease seizure frequency.
      - Vigabatrin and rufinamide are effective for decreasing seizure frequency, but are not first-line agents.

- Ezogabine (no longer marketed) use should be considered to reduce seizure frequency, but carries a serious risk of skin and retinal discoloration.
- Clobazam and extended-release oxcarbazepine may be considered to decrease seizure frequency.

▪ As monotherapy in patients with TRAFE:
- Eslicarbazepine use may be considered to decrease seizure frequency.
- Data are insufficient to recommend use of second- and the other third-generation AEDs.

▪ For add-on therapy for generalized epilepsy, immediate-release and extended-release lamotrigine should be considered as add-on therapy to decrease seizure frequency in adults with treatment-resistant generalized tonic-clonic seizures secondary to generalized epilepsy. Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for treatment-resistant generalized tonic-clonic seizures and for treatment-resistant juvenile myoclonic epilepsy.

▪ Rufinamide is effective to reduce seizure frequency as add-on therapy for LGS. Clobazam use should be considered as add-on therapy for LGS.

▪ For add-on therapy in pediatric patients with treatment-resistant focal epilepsy:
- Levetiracetam use should be considered to decrease seizure frequency (ages 1 month to 16 years).
- Zonisamide use should be considered to decrease seizure frequency (age 6 to 17 years).
- Oxcarbazepine use should be considered to decrease seizure frequency (age 1 month to 4 years).
- Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, rufinamide, tiagabine, or vigabatrin.

▪ The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.

- **Evidence-based guideline: management of an unprovoked first seizure in adults.** Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (*Krumholz et al 2015; reaffirmed in 2018*).
  - This practice guideline makes recommendations based on a consideration of the evidence for prognosis and treatment of adults with an unprovoked first seizure.
  - Recommendations include the following:
    - Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21% to 45%).
    - Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, or a nocturnal seizure.
    - Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure, it may not improve quality of life.
    - Clinicians should advise patients that over the longer term (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission.
    - Patients should be advised that their risk for AED AEs ranges from 7% to 31% and that these AEs are predominantly mild and reversible.
  - Immediate AED therapy after an unprovoked first seizure is likely to reduce seizure recurrence risk. A reduction in risk may be important, particularly for adults, for whom seizure recurrences may cause serious psychological and social consequences such as loss of driving privileges and limitations on employment. However, immediate AED treatment is not well accepted and is debated. Decisions should be based on weighing the risk of recurrence against the AEs of AED therapy, and should take patient preferences into account.
  - It is accepted that when a patient has a second or additional seizures, an AED should be initiated because the risk of subsequent seizures is very high.
- **Evidence-based guideline: treatment of convulsive status epilepticus in children and adults.** Guideline Committee of the American Epilepsy Society (*Glauser et al 2016*).
  - This publication provides conclusions and a treatment algorithm based on a structured literature review of randomized trials of anticonvulsant treatments for seizures lasting longer than 5 minutes. A total of 38 trials were included.
  - For treatment in the adult population, conclusions included the following:
    - Intramuscular (IM) midazolam, intravenous (IV) lorazepam, IV diazepam (with or without phenytoin), and IV phenobarbital are established as efficacious at stopping seizures lasting at least 5 minutes.
    - IV lorazepam is more effective than IV phenytoin in stopping seizures lasting at least 10 minutes.

        - There is no difference in efficacy between IV lorazepam followed by IV phenytoin, IV diazepam plus phenytoin followed by IV lorazepam, and IV phenobarbital followed by IV phenytoin.
        - IV valproic acid has similar efficacy to IV phenytoin or continuous IV diazepam as second therapy after failure of a benzodiazepine.
        - Insufficient data exist in adults about the efficacy of levetiracetam as either initial or second therapy.
        - In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam.
        - No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus.
    - For treatment in the pediatric population, conclusions included the following:
        - IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 minutes.
        - Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 minutes.
        - Insufficient data exist in children about the efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy.
        - IV valproic acid has similar efficacy but better tolerability than IV phenobarbital as second therapy after failure of a benzodiazepine.
        - Insufficient data exist in children regarding the efficacy of phenytoin or levetiracetam as second therapy after failure of a benzodiazepine.
        - In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam.
        - In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal).
    - Conclusions included the following (age not specified):
        - Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin. Fosphenytoin is better tolerated compared with phenytoin. When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative.
    - The overall treatment algorithm directs that:
        - A benzodiazepine (IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice in the first phase of treatment (5 to 20 minutes after the beginning of the seizure). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration positions it as an alternative initial therapy. For prehospital settings or where first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives.
        - In the second phase of treatment (from 20 to 40 minutes after the beginning of the seizure), reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any of these options is better than the others. Because of AEs, IV phenobarbital is a reasonable second-therapy alternative if none of the 3 recommended therapies are available.
        - There is no clear evidence to guide therapy in the third phase of therapy (≥ 40 minutes after the beginning of the seizure).
- **Evidence-based guideline update: medical treatment of infantile spasms.** Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Go et al 2012*; reaffirmed in 2018)
    - This publication provides updated recommendations for the treatment of infantile spasms. The literature review included an evaluation of 26 published articles on this topic.
    - Recommendations include the following:
        - Evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as adrenocorticotropic hormone (ACTH) for short-term treatment of infantile spasms.
        - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms.
        - ACTH or vigabatrin may be offered for short-term treatment of infantile spasms; evidence suggests that ACTH may be offered over vigabatrin.

        - Evidence is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam [not available in the United States], levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms.
        - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome.
        - A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
    - There is a lack of sufficient randomized trials to provide definitive answers to key questions related to treatment of infantile spasms.
- **Practice parameter: treatment of the child with a first unprovoked seizure.** Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Hirtz et al 2003*; reaffirmed in 2018)
    - This parameter reviews published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations. Treatment during the neonatal period is not addressed.
    - Recommendations include the following:
        - Treatment with AEDs is not indicated for the prevention of the development of epilepsy.
        - Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial AEs.
    - The majority of children who experience a first unprovoked seizure will have few or no recurrences. Treatment with AEDs after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission.
    - Treatment has been shown in several studies combining both children and adults to reduce the risk of seizure recurrence; however, there is a relative paucity of data from studies involving only children after a first seizure.
- **Summary of recommendations for the management of infantile seizures**. Task force report for the ILAE Commission of Pediatrics (*Wilmshurst et al 2015*).
    - This publication recommends an approach to the standard and optimal management of infants with seizures. When possible, recommendations are evidence-based; however, when no evidence was available, recommendations are based on expert opinion and standard practice.
    - Recommendations/findings include the following:
        - There is no indication for initiation of chronic AEDs for simple febrile seizures. However, in the acute treatment of febrile seizures, it is important to treat seizures lasting 10 minutes or longer.
        - In an otherwise healthy infant, a policy of “wait and see” is reasonable after the first afebrile seizure. However, this is a rare event and close monitoring is essential.
        - Treatment options with established or probable efficacy include the following:
            - Focal seizures: levetiracetam
            - Epileptic spasms: High-dose or low-dose ACTH
            - Dravet syndrome: stiripentol
        - Treatment options with possible efficacy include the following:
            - Generalized seizures: levetiracetam, valproate, lamotrigine, topiramate, clobazam
            - Epileptic spasms: prednisone, vigabatrin
            - Benign infantile convulsions: carbamazepine, phenobarbital, valproate
            - Dravet syndrome: topiramate, zonisamide, valproate
            - Benign myoclonic epilepsy of infancy: valproate, topiramate, lamotrigine, clonazepam
            - Provoked or situational seizures: carbamazepine
        - There is no clear evidence supporting an optimal duration of treatment; this is dependent on seizure type.
- **Guidelines on neonatal seizures**. World Health Organization (WHO) (*WHO 2011*).
    - This document was prepared based on a systematic review of the literature and involved cooperation between the WHO, the ILAE, and the International Bureau of Epilepsy (IBE).
    - Recommendations include the following:
        - Phenobarbital should be used as the first-line agent for treatment of neonatal seizures and should be made readily available in all settings.

        - In neonates who continue to have seizures despite administering the maximum tolerated dose of phenobarbital, either a benzodiazepine, phenytoin, or lidocaine may be used as the second-line agent for control of seizures (use of phenytoin or lidocaine requires cardiac monitoring).
        - In neonates with a normal neurological examination and/or normal EEG, stopping AEDs may be considered if the neonate has been seizure-free for > 72 hours; the drug(s) should be reinstituted if seizures recur.
        - In neonates in whom seizure control is achieved with a single AED, the drug can be discontinued abruptly without tapering the dose. In neonates requiring > 1 AED for seizure control, the drugs may be stopped one at a time, with phenobarbital being the last drug to be withdrawn.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009A*; reaffirmed in 2013; Update in progress)
    - This publication summarizes evidence for selected issues regarding the clinical management of women with epilepsy (WWE) who are pregnant or planning to be pregnant.
    - Recommendations include the following:
        - If possible, avoidance of the use of valproate as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (MCMs).
        - If possible, avoidance of the use of valproate monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs.
        - To reduce the risk of MCMs, the use of valproate during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine.
        - To reduce the risk of MCMs, avoidance of the use of polytherapy with valproate during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without valproate.
        - To reduce the risk of MCMs, avoidance of the use of valproate during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin or lamotrigine.
        - To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered.
        - Limiting the dosage of valproate or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of MCMs.
        - Avoidance of the use of valproate, if possible, should be considered to reduce the risk of neural tube defects and facial clefts, and may be considered to reduce the risk of hypospadias.
        - Avoidance of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for phenytoin use, posterior cleft palate for carbamazepine use, and cardiac malformations for phenobarbital use.
        - Carbamazepine exposure probably does not produce cognitive impairment in offspring of WWE.
        - Avoiding valproate in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes.
        - Avoiding phenytoin and phenobarbital in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes.
        - Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes.
        - For WWE who are pregnant, avoidance of valproate, if possible, should be considered compared to carbamazepine to reduce the risk of poor cognitive outcomes.
        - For WWE who are pregnant, avoidance of valproate, if possible, may be considered compared to phenytoin to reduce the risk of poor cognitive outcomes.
    - Valproate has the most data showing an association with risk from in utero exposure. If a change from valproate to another AED is planned, it is prudent to make this change well before pregnancy.
    - Although many of the recommendations in this parameter suggest minimizing AED exposure during pregnancy, for most WWE, discontinuing AEDs is not a reasonable or safe option. Discontinuing AEDs may expose the mother and fetus to physical injury from accidents due to seizure activity.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding.** Quality Standards Subcommittee and

Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009B*; reaffirmed in 2013; Update in progress)
- This publication summarizes evidence for selected issues regarding the clinical management of WWE who are pregnant or planning to be pregnant.
- Recommendations include the following:
  - The fact that phenobarbital, primidone, phenytoin, carbamazepine, levetiracetam, valproate, gabapentin, lamotrigine, oxcarbazepine, and topiramate cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy.
  - Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered.
  - Monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels during pregnancy may be considered.
  - There is insufficient evidence to support or refute a change in phenobarbital, valproate, primidone, or ethosuximide levels related to pregnancy, but this lack of evidence should not discourage monitoring levels of these AEDs during pregnancy.
  - Valproate, phenobarbital, phenytoin, and carbamazepine may not transfer into breast milk to as great an extent as primidone, levetiracetam, gabapentin, lamotrigine, and topiramate.
- Although many of the AEDs were shown to cross the placenta or enter breast milk, studies were limited in duration and did not systematically evaluate neonatal symptoms.

- Guidelines also support the use of AEDs for several common non-epilepsy indications:
  - The American Academy of Neurology and American Headache Society state that AEDs with established efficacy for migraine prevention include valproate, divalproex sodium, and topiramate; carbamazepine is noted to be possibly effective (*Silberstein et al 2012;* reaffirmed in 2015; Update in progress). An American Academy of Neurology guideline for pediatric migraine prevention noted that children and adolescents with migraine receiving topiramate are probably more likely than those receiving placebo to have a reduction in migraine or headache day frequency, whereas there was insufficient evidence to support the efficacy of extended-release divalproex sodium for reducing frequency (*Oskoui et al 2019*).
  - The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation state that, for relief of painful diabetic neuropathy, pregabalin is established as effective, and gabapentin and valproate are probably effective (*Bril et al 2011*; Update in progress).
  - A retired guideline from The American Academy of Neurology states that gabapentin and pregabalin are of benefit in reducing pain from postherpetic neuralgia (*Dubinsky et al 2004; retired February 27, 2018*).
  - American Psychiatric Association guidelines describe the key role of AEDs in the management of bipolar disorder, including the following (*Hirschfeld et al 2002*):
    - First-line pharmacological treatment for more severe manic or mixed episodes is either lithium plus an antipsychotic or valproate plus an antipsychotic; for less ill patients, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. For mixed episodes, valproate may be preferred over lithium. Carbamazepine and oxcarbazepine are alternatives.
    - First-line pharmacological treatment for bipolar depression is either lithium or lamotrigine. When an acute depressive episode of bipolar disorder does not respond to first-line medication treatment, the next steps include adding lamotrigine, bupropion, or paroxetine.
    - The initial treatment for patients who experience rapid cycling should include lithium or valproate; an alternative is lamotrigine.
    - The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine.
    - Note: This guideline was published in 2002 and cannot be assumed to be current; however, AEDs continue to be recommended for both acute (mania or hypomania) and maintenance phases of bipolar disorder *(Post 2017, Stovall 2018).*

SAFETY SUMMARY

- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment (*Schachter 2019*).

- Common AEs among AEDs include the following (*Fintepla prescribing information 2020, Schachter 2019*):
  - Systemic AEs:
    - nausea, vomiting, constipation, diarrhea, anorexia
    - rash
    - hyponatremia (carbamazepine, eslicarbazepine, oxcarbazepine)
    - weight gain (pregabalin, perampanel, valproate), weight loss (felbamate, topiramate, stiripentol, fenfluramine)
  - Neurologic AEs:
    - headache
    - somnolence, sedation, drowsiness, lethargy, fatigue
    - dizziness, vertigo
    - tremor, anxiety, nervousness, insomnia
    - aggression, irritability, hyperactivity
    - depression, mood alteration
    - confusion
    - ataxia
    - blurred or double vision
- Examples of rare but serious AEs include the following (*Schachter 2019, individual package inserts*):
  - suicidal ideation and behavior (AEDs as a class, except everolimus)
  - neutropenia, leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, and/or aplastic anemia (brivaracetam, carbamazepine, ethosuximide, felbamate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, primidone, stiripentol, valproate, vigabatrin, zonisamide)
  - anaphylaxis or angioedema (brivaracetam, fosphenytoin, gabapentin, levetiracetam, phenytoin, pregabalin)
  - severe skin rashes, Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN) (carbamazepine, clobazam, eslicarbazepine, ethosuximide, fosphenytoin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide, tiagabine, topiramate, valproate, zonisamide)
  - hepatic failure (carbamazepine, ethosuximide, felbamate, phenytoin, phenobarbital, primidone, valproate)
  - hepatocellular injury (cannabidiol)
  - prolonged PR interval, atrioventricular block, and/or changes in QT interval (cenobamate, eslicarbazepine, lacosamide, rufinamide)
  - serum sickness (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate)
  - multiorgan hypersensitivity (carbamazepine, cenobamate, ethosuximide, gabapentin, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, valproate, zonisamide)
  - severe neuropsychiatric effects/hostility/aggression (brivaracetam, levetiracetam, perampanel)
  - hemophagocytic lymphohistiocytosis (HLH) (lamotrigine)
  - cardiac AEs, including bradycardia and cardiac arrest (phenytoin)
  - abnormal magnetic resonance imaging signals in infants (vigabatrin)
  - intramyelinic edema (vigabatrin)
  - serotonin syndrome (fenfluramine)
  - significant elevation in blood pressure including hypertensive crisis (fenfluramine)
- A number of AEDs carry boxed warnings related to potentially serious AEs; these include the following:
  - Carbamazepine:
    - Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Patients with ancestry in genetically at-risk populations (across broad areas of Asia) should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
    - Aplastic anemia and agranulocytosis have been reported. If a patient exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely, and discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.
  - Clobazam, clonazepam, clorazepate, diazepam, and midazolam:
    - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Concomitant prescribing should be reserved for use in patients for whom alternative

treatment options are inadequate, and patients should be followed for signs and symptoms of respiratory depression and sedation.

- Felbamate:
  - Use is associated with a marked increase in the incidence of aplastic anemia. Felbamate should only be used in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but it will in some cases allow detection of hematologic changes before the syndrome declares itself clinically. Felbamate should be discontinued if any evidence of bone marrow depression occurs.
  - Cases of acute liver failure have been reported. Felbamate should not be prescribed for anyone with a history of hepatic dysfunction. Treatment should be initiated only in individuals without active liver disease and with normal baseline serum transaminases. It has not been proven that periodic serum transaminase testing will prevent serious injury, but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Serum transaminases should be monitored at baseline and periodically thereafter. Felbamate should be discontinued if either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) become increased to ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure, and should not be considered for retreatment.
- Fenfluramine:
  - Use of serotonergic drugs with 5-HT2B receptor agonist activity (eg, fenfluramine) is associated with valvular heart disease and pulmonary arterial hypertension. Echocardiogram assessments are required before, during, and after treatment with fenfluramine, and the benefits vs risks of initiating or continuing treatment with this product must be considered based on echocardiogram findings.
  - Due to the risks of valvular heart disease and pulmonary arterial hypertension, fenfluramine is available only through a risk evaluation and mitigation strategy (REMS) program (*FDA REMS 2020*). Healthcare providers who prescribe fenfluramine and pharmacies that dispense the product must be certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic cardiovascular monitoring is performed and report any AE suggestive of valvular heart disease and/or pulmonary hypertension to the fenfluramine REMS program.
- Fosphenytoin and phenytoin:
  - There is a cardiovascular risk associated with rapid IV infusion rates. The rate of administration should not exceed recommendations, and careful cardiac monitoring is required.
- Lamotrigine:
  - Cases of life-threatening serious skin rashes, including SJS and TEN, and/or rash-related death have been caused by lamotrigine. Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious. Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related.
- Perampanel:
  - Serious or life-threatening psychiatric and behavioral AEs including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported. Patients should be monitored for these reactions and for changes in mood, behavior, or personality. The dose should be reduced if these symptoms occur, and it should be discontinued if symptoms are severe or worsening.
- Valproic acid and divalproex sodium:
  - Hepatotoxicity, including fatalities, have been reported, usually during the first 6 months of treatment. Serum liver tests are required and patients should be monitored closely. There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with mitochondrial disease. Valproic acid and divalproex sodium are contraindicated in patients known to have mitochondrial disorders caused by polymerase gamma (POLG) gene mutations, and in children < 2 years of age who are suspected of having a mitochondrial disorder.
  - There is a risk to fetuses exposed in utero, particularly neural tube defects, other major malformations, and decreased intelligence quotient (IQ). Valproate should not be given to a woman of childbearing potential unless the drug is essential to the management of her medical condition, and women should use effective contraception while using valproate.
  - Pancreatitis, including fatal hemorrhagic cases, has occurred. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation.

- Vigabatrin:
  - Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin may also damage the central retina and may decrease visual acuity. Baseline and periodic vision assessment are recommended. However, this assessment cannot always prevent vision damage, and once detected, vision loss due to vigabatrin is not reversible. Vigabatrin should be withdrawn from patients who fail to show substantial clinical benefit.
  - Due to the risks of vision loss, vigabatrin is available only through a REMS program (*FDA REMS 2020*). Healthcare providers who prescribe vigabatrin and pharmacies that dispense the product must be specially certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic visual monitoring is performed and report any AE suggestive of vision loss to the vigabatrin REMS program.

- Everolimus is an antineoplastic, immunosuppressant agent associated with several AEs.
  - The most common AE that occurred in trials for TSC-associated partial-onset seizures was stomatitis.
  - More serious AEs include:
    - non-infectious pneumonitis
    - infections
    - hypersensitivity reactions
    - angioedema (when taken with an angiotensin-converting enzyme inhibitor)
    - renal failure
    - impaired wound healing
    - myelosuppression
    - reduced immune response with vaccination
    - hyperglycemia
    - hyperlipidemia
    - embryo-fetal toxicity

DOSING AND ADMINISTRATION

- General dosing information is provided in Table 3. Dosing may vary based on the specific indication, interacting medications, and the patient's age and renal and hepatic function. Additionally, some medications are recommended to be titrated during initial treatment. Please refer to the prescribing information of the individual products for more detailed information.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Barbiturates				
Pentobarbital (Nembutal)	injection	IV, IM	Single dose	Acute use only. If needed, additional small increments may be given after the initial dose.
Phenobarbital* (Luminal†, Solfoton†)	tablets, elixir, injection	oral, IV, IM	2 to 3 times per day	
Primidone (Mysoline)	tablets	oral	3 to 4 times per day	
Benzodiazepines				
Clobazam (Onfi, Sympazan)	tablets, oral suspension, oral film	oral	1 or 2 times per day	Daily doses > 5 mg should be given in divided doses 2 times per day. Sympazan should be applied on top of the tongue where it adheres and dissolves.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Clonazepam (Klonopin)	tablets, orally disintegrating tablets (wafers)	oral	3 times per day	
Clorazepate (Tranxene T-Tab)	tablets	oral	2 to 3 times per day	
Diazepam (Diastat, Valium, Valtoco)	tablets, oral solution, oral concentrate, rectal gel, injection, nasal spray	oral, rectal, IV, IM, intranasal	2 to 4 times per day	For the rectal gel (for acute use), a second dose may be given 4 to 12 hours after the initial dose when required. The injection and nasal spray are also for short-term acute use. For the nasal spray, a second dose may be given 4 hours after the initial dose when required. The product should be used to treat no more than 1 episode every 5 days and no more than 5 episodes per month.
Midazolam (Nayzilam)	nasal spray	intranasal	Up to 2 doses per seizure cluster, with the second dose given at least 10 minutes after the first dose	Should be used to treat no more than 1 episode every 3 days and no more than 5 episodes per month.
Hydantoins				
Ethotoin (Peganone)	tablets	oral	4 to 6 times per day	
Fosphenytoin (Cerebyx)	injection	IV, IM	2 times per day or other divided doses based on drug levels	Generally used in acute situations as a loading dose; may be given in divided doses when substituted for oral phenytoin.
Phenytoin (Dilantin, Phenytek)	extended-release capsules, chewable tablets, oral suspension, injection	oral, IV, IM	2 to 4 times per day	Capsules are extended-release and may be suitable for once-daily dosing in some adults.
Miscellaneous				
Brivaracetam (Briviact)	tablets, oral solution, injection	oral, IV	2 times per day	The injection may be used when oral administration is temporarily not feasible.
Cannabidiol (Epidiolex)	oral solution	oral	2 times per day	The provided oral syringe should be used to measure an accurate dose.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	tablets, chewable tablets, oral suspension, extended-release tablets, extended-release capsules	oral	2 to 4 times per day	Immediate-release tablets are given 2 to 3 times per day and the suspension is given 4 times per day. Carbatrol and Equetro are twice-daily

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				extended-release capsule formulations; these capsules may be opened and sprinkled on soft food. Tegretol-XR is a twice-daily extended-release tablet formulation; these tablets must be swallowed whole.
Cenobamate (Xcopri)	tablets	oral	once daily	The recommended titration schedule should not be exceeded.
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	delayed-release tablets, delayed-release sprinkle capsules, extended-release tablets	oral	2 to 3 times per day (once daily for extended-release tablets)	Delayed-release tablets and extended-release tablets should be swallowed whole. Sprinkle capsules may be opened and sprinkled on soft food. Delayed-release tablet and capsule doses > 250 mg per day should be given in divided doses.
Eslicarbazepine (Aptiom)	tablets	oral	once daily	Tablets may be crushed.
Ethosuximide (Zarontin)	capsules, oral solution/syrup	oral	once daily or in divided doses	
Everolimus (Afinitor Disperz)	tablets for oral suspension	oral	once daily	Should be taken at the same time each day with or without food. Suspension should be prepared using water only and administered immediately after preparation. The suspension should be discarded if not taken within 60 minutes of preparation. Dose adjustments are made based on trough drug concentration.
Felbamate (Felbatol)	tablets, oral suspension	oral	3 or 4 times per day	
Fenfluramine (Fintepla)	oral solution	oral	2 times per day	
Gabapentin (Neurontin)	tablets, capsules, oral solution	oral	3 times per day	Capsules should be swallowed whole.
Lacosamide (Vimpat)	tablets, oral solution, injection	oral, IV	2 times per day	
Lamotrigine (Lamictal, Lamictal ODT,	tablets, chewable dispersible tablets, orally disintegrating tablets, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	Only whole tablets should be administered. Extended-release tablets must not be chewed or crushed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Lamictal XR, Subvenite)				
Levetiracetam (Keppra, Keppra XR, Roweepra, Roweepra XR, Spritam, Elepsia XR)	tablets, tablets for oral suspension, oral solution, extended-release tablets, injection	oral, IV	2 times per day (once daily for extended-release tablets)	Tablets and extended-release tablets should not be chewed or crushed. Tablets for oral suspension (Spritam) can be dissolved in liquid and swallowed or allowed to disintegrate in the mouth.
Methsuximide (Celontin)	capsules	oral	3 to 4 times per day (*Lexicomp 2020*)	
Oxcarbazepine (Oxtellar XR, Trileptal)	tablets, oral suspension, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	In conversion of oxcarbazepine immediate-release to Oxtellar XR, higher doses of Oxtellar XR may be necessary. Extended-release tablets must not be chewed or crushed.
Perampanel (Fycompa)	tablets, oral suspension	oral	once daily at bedtime	
Pregabalin (Lyrica)	capsules, oral solution	oral	2 to 3 times per day	
Rufinamide (Banzel)	tablets, oral suspension	oral	2 times per day	Tablets can be administered whole, as half tablets, or crushed.
Stiripentol (Diacomit)	capsules, powder for oral suspension	oral	2 to 3 times per day	Capsules must be swallowed whole with a glass of water during a meal. Powder should be mixed with water and taken immediately after mixing during a meal.
Tiagabine (Gabitril)	tablets	oral	2 to 4 times per day	
Topiramate (Topamax, Topamax Sprinkle, Topiragen, Trokendi XR, Qudexy XR)	tablets, sprinkle capsules, extended-release capsules, extended-release sprinkle capsules	oral	2 times per day (once daily for extended-release capsule formulations)	Sprinkle capsules may be opened and sprinkled on soft food. Extended-release capsules (Trokendi XR) must not be chewed or crushed, but extended release sprinkle capsules (Qudexy XR) may be sprinkled on soft food.
Valproic acid/ valproate sodium (Depakene†, Depacon†)	capsules, oral solution/ syrup, injection	oral, IV	1 to 3 times per day (*Lexicomp 2020*)	Capsules should be swallowed whole without chewing to avoid local irritation of the mouth and throat. If the total dose exceeds 250 mg, it should be given in divided doses.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Vigabatrin (Sabril, Vigadrone)	tablets, powder for oral solution	oral	2 times per day	Powder for oral solution is supplied in individual dose packets to be mixed with water before administration.
Zonisamide (Zonegran)	capsules	oral	1 or 2 times per day	Capsules must be swallowed whole.

* Not FDA approved
† Brand product not currently marketed; generic is available

CONCLUSION

- Several classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents. These products vary in terms of their indications for specific seizure types and indications other than epilepsy.
- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. When possible, monotherapy with a single AED is the preferred treatment approach.
- Patients who are refractory to monotherapy may be treated with combination therapy. When considering combination therapy, it is recommended to combine medications with different mechanisms of action and AE profiles.
- Comparative efficacy data for the management of epilepsy are limited.
- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment. Both systemic AEs and neurologic AEs commonly occur. Some AEDs are associated with rare but serious AEs, and careful patient selection and monitoring are required.
- Epilepsy management can be complex and is often performed by neurologists. A variety of AEDs should be available to allow clinicians to select the most clinically appropriate agent for individual patients.
- Anticonvulsants are also established as effective for several non-epilepsy indications, including (but not limited to) bipolar disorder, migraine prophylaxis, and neuropathic pain.

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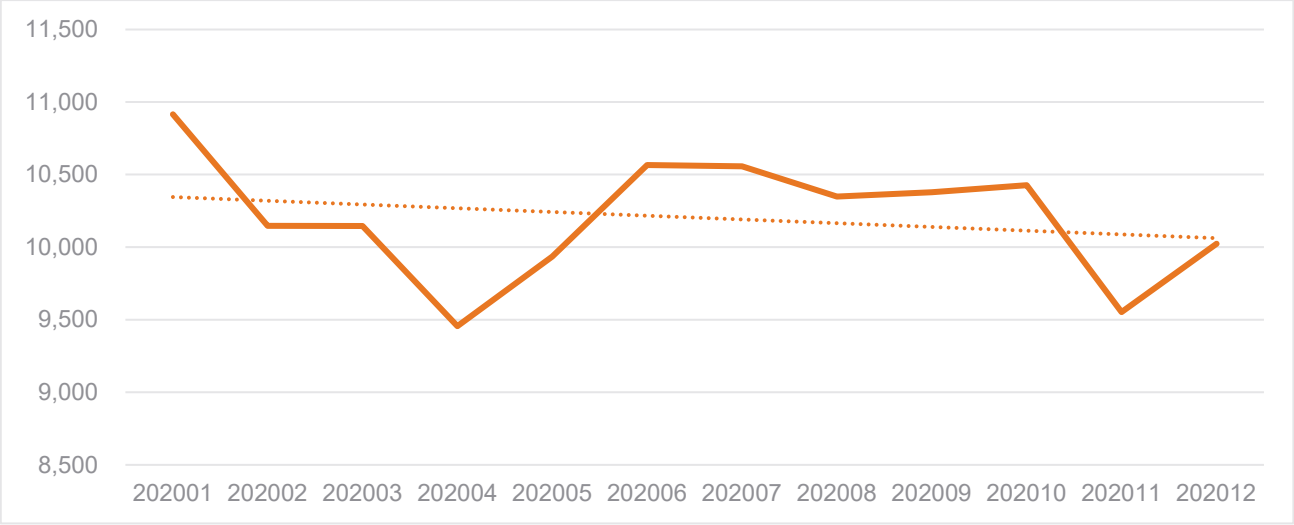
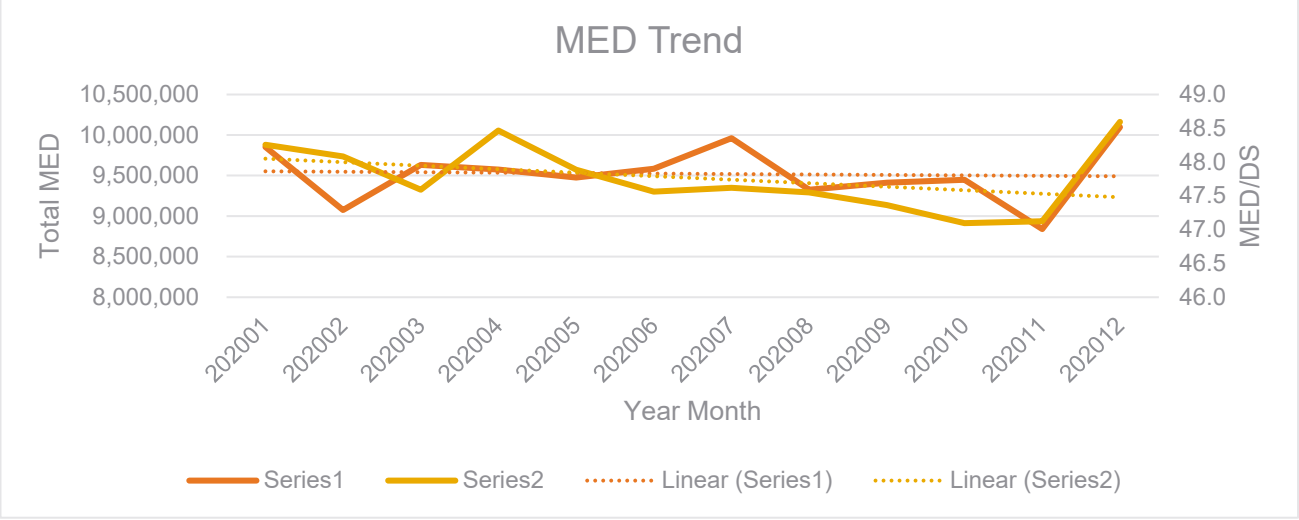
Board Requested Reports

Nevada Medicaid

Opioid Trends
Fee for Service
January 1, 2020 - December 31, 2020

Date Filled	Count of Claims	Days Supply	Count of Members	Total Qty	Total MED	MED per DS
202001	10,916	204,173	9,440	690,568	9,852,457	48.3
202002	10,147	188,741	9,007	632,690	9,075,028	48.1
202003	10,145	202,390	8,774	681,122	9,631,513	47.6
202004	9,456	197,538	8,243	660,514	9,573,722	48.5
202005	9,935	197,869	8,651	660,507	9,475,041	47.9
202006	10,565	201,483	9,094	676,285	9,583,039	47.6
202007	10,557	209,174	9,059	704,609	9,960,391	47.6
202008	10,348	196,110	9,072	659,967	9,325,026	47.5
202009	10,378	198,707	9,081	672,432	9,411,303	47.4
202010	10,427	200,603	9,064	670,255	9,447,720	47.1
202011	9,552	187,589	8,433	628,308	8,839,780	47.1
202012	10,023	207,782	8,600	699,686	10,097,082	48.6





Nevada Medicaid

Opioid Trends - Top Ten Members

Fee for Service

October 1, 2020 - December 31, 2020

Member ID Encrypted	Count of Claims	Days Supply	Total Quantity	Total MED
77771952964	6	180	600	81,000
33330458115	7	206	1,182	67,800
71367188889	8	240	840	57,600
44446597311	6	180	585	56,700
50155177779	8	240	1,440	54,000
11110100737	9	254	1,500	52,200
22222296971	8	120	1,480	50,400
44448546720	7	194	1,350	48,150
49044066667	6	172	946	46,440
76050522223	6	180	720	45,900

Member ID Encrypted	Drug Label Name	Count of Claims	Days Supply	Total Quantity
11110100737	MORPHINE SUL TAB 100MG	3	84	360
11110100737	OXYCODONE TAB 30MG	3	86	360
11110100737	METHADONE TAB 10MG	3	84	780
11110100737 Total		**9**	**254**	**1,500**
22222296971	FENTANYL DIS 100MCG/H	4	60	40
22222296971	OXYCODONE TAB 10MG	4	60	1,440
22222296971 Total		**8**	**120**	**1,480**
33330458115	MORPHINE SUL TAB 100MG	4	116	462
33330458115	OXYCODONE TAB 20MG	3	90	720
33330458115 Total		**7**	**206**	**1,182**
44446597311	FENTANYL DIS 100MCG/H	3	90	45
44446597311	OXYCODONE TAB 30MG	2	60	360
44446597311 Total		**5**	**150**	**405**
44448546720	HYDROCO/APAP TAB 10-32	4	120	360
44448546720	OXYCODONE TAB 30MG	3	74	990
44448546720 Total		**7**	**194**	**1,350**
49044066667	OXYCODONE TAB 30MG	3	86	688
49044066667	MORPHINE SUL TAB 60MG	3	86	258
49044066667 Total		**6**	**172**	**946**
50155177779	OXYCODONE TAB 30MG	4	120	720
50155177779	MORPHINE SUL TAB 30MG	4	120	720
50155177779 Total		**8**	**240**	**1,440**
71367188889	OXYCODONE TAB 30MG	4	120	480
71367188889	MORPHINE SUL TAB 100MG	4	120	360
71367188889 Total		**8**	**240**	**840**
76050522223	OXYCODONE TAB 30MG	3	90	540
76050522223	OXYCONTIN TAB 80MG C	3	90	180
76050522223 Total		**6**	**180**	**720**
77771952964	OXYCODONE TAB 30MG	2	60	360
77771952964	FENTANYL DIS 100MCG/H	3	90	90
77771952964	METHADONE TAB 10MG	1	30	150
77771952964 Total		**6**	**180**	**600**
Grand Total		**70**	**1,936**	**10,463**

Nevada Medicaid

Fee for Service - Opioid Trends - Top Ten Prescribers

By Morphine Equivalent Dose (MED)

Quarter Filled	Prescriber ID	City	Degree	Specialty	Count of Members	Count of Claims	Total Days Supply	Total Qty	Total MED	MED/ DS	MED/DS/ Member
2020 Q4	P	SPARKS	MD	- Anesthesiology	108	286	8,372	24,326	615,740	73.55	0.68
2020 Q4	V	LAS VEGAS	MD	- Anesthesiology	199	354	9,359	31,744	539,729	57.67	0.29
2020 Q4	F	LAS VEGAS	PAC	- Orthopedic Surgery	170	326	9,476	32,410	485,594	51.24	0.30
2020 Q4	HH	LAS VEGAS	PAC	- Physician Assistant	111	231	6,609	21,951	458,528	69.38	0.63
2020 Q4	S	LAS VEGAS	NP	- Nurse Practioner	170	295	8,111	27,532	454,244	56.00	0.33
2020 Q4	AA	LAS VEGAS	NP	- Nurse Practioner	104	210	5,862	19,180	454,068	77.46	0.74
2020 Q4	JJ	LAS VEGAS	NP	- Nurse Practioner	107	237	6,969	21,064	430,086	61.71	0.58
2020 Q4	FF	HENDERSON	MS	- Physician Assistant	98	203	5,549	18,989	424,609	76.52	0.78
2020 Q4	U	LAS VEGAS	PAC	- Physician Assistant	154	316	9,312	31,784	422,935	45.42	0.29
2020 Q4	H	HENDERSON	PAC	- Physician Assistant	44	90	2,654	9,927	385,965	145.43	3.31
2020 Q3	A	RENO	DO	- Anesthesiology	138	374	11,373	46,445	628,366	55.25	0.40
2020 Q3	P	SPARKS	MD	- Anesthesiology	108	264	7,753	22,268	536,382	69.18	0.64
2020 Q3	F	LAS VEGAS	PAC	- Orthopedic Surgery	176	375	10,816	34,987	513,172	47.45	0.27
2020 Q3	HH	LAS VEGAS	PAC	- Physician Assistant	88	229	6,487	21,743	501,870	77.37	0.88
2020 Q3	U	LAS VEGAS	PAC	- Physician Assistant	145	371	10,942	37,051	492,020	44.97	0.31
2020 Q3	V	LAS VEGAS	MD	- Anesthesiology	134	282	7,738	26,210	442,113	57.14	0.43
2020 Q3	AA	LAS VEGAS	NP	- Nurse Practioner	97	203	5,541	17,911	433,129	78.17	0.81
2020 Q3	H	HENDERSON	PAC	- Physician Assistant	45	100	2,920	10,875	431,775	147.87	3.29
2020 Q3	S	LAS VEGAS	NP	- Nurse Practioner	139	289	7,567	26,214	430,986	56.96	0.41
2020 Q3	JJ	LAS VEGAS	NP	- Nurse Practioner	105	247	7,263	22,515	414,693	57.10	0.54

By Morphine Equivalent Dose (MED) Per Member Per Day Supply

Quarter Filled	Prescriber ID	City	Degree	Specialty	Count of Members	Count of Claims	total Days Supply	Total Qty	Total MED	MED/ DS	MED/DS/ Member
2020 Q4	I	HENDERSON	DO	- Internal Medicine	1	3	90	360	16,200	180.00	180.00
2020 Q4	DD	RENO	NP	- Primary Care	1	1	10	90	1,800	180.00	180.00
2020 Q4	GG	SOUTH LAKE TAHOE	MD	- Emergency Medicine	1	1	12	4	2,160	180.00	180.00
2020 Q4	R	HENDERSON	MD	- Internal Medicine	1	2	10	40	1,800	180.00	180.00
2020 Q4	M	LAS VEGAS	MD	- Family Medicine	1	1	10	40	1,800	180.00	180.00
2020 Q4	II	HENDERSON	NP	- Nurse Practitioner	1	7	20	200	3,000	150.00	150.00
2020 Q4	Y	SALT LAKE CITY	NP	- Nurse Practitioner	1	1	3	14	420	140.00	140.00
2020 Q4	X	LAS VEGAS	MD	- Specialist	2	5	150	930	41,850	279.00	139.50
2020 Q4	D	LAS VEGAS	-	- Resident	1	1	6	36	810	135.00	135.00
2020 Q4	Z	LAS VEGAS	DO	- Internal Medicine	1	2	60	180	8,100	135.00	135.00
2020 Q4	N	RENO	MD	- Internal Medicine	1	1	30	180	4,050	135.00	135.00
2020 Q4	EE	HENDERSON	MD	- Internal Medicine	1	1	11	33	1,485	135.00	135.00
2020 Q3	O	RENO	MD	- Radiology	1	2	24	240	3,600	150.00	150.00
2020 Q3	X	LAS VEGAS	MD	- Specialist	2	6	180	1,110	49,950	277.50	138.75
2020 Q3	C	LAS VEGAS	DO	- Hospitalist	1	2	60	180	8,100	135.00	135.00
2020 Q3	E	CARSON CITY	MD	- Family Medicine	1	1	14	42	1,890	135.00	135.00
2020 Q3	B	EAST MEADOW	MD	- Internal Medicine	1	1	3	18	405	135.00	135.00
2020 Q3	L	CARSON CITY	MD	- Radiology	1	1	14	120	1,800	128.57	128.57
2020 Q3	G	PAHRUMP	MD	- Internal Medicine	1	3	90	360	10,800	120.00	120.00
2020 Q3	W	MINNEAPOLIS	MSN	- Nurse Practitioner	1	1	30	120	3,600	120.00	120.00
2020 Q3	K	RENO	APN	- Registered Nurse	1	1	30	10	3,600	120.00	120.00
2020 Q3	T	LAS VEGAS	DO	- Internal Medicine	2	6	180	1,080	40,500	225.00	112.50
2020 Q3	BB	NORTH LAS VEGAS	MSN	- Registered Nurse	1	1	30	75	3,375	112.50	112.50
2020 Q3	CC	LAS VEGAS	MD	- Internal Medicine	1	3	90	450	10,125	112.50	112.50

Standard DUR Reports

Nevada Medicaid

Top Ten Therapeutic Classes

Fee for Service

July 1, 2020 - December 31, 2020

Top 10 Classes by Claim Count

2020 Q4

Drug Class Name	Count of Claims	Amt Paid
ANTICONVULSANTS - MISC.	27,055	$ 2,722,609.26
SYMPATHOMIMETICS	18,738	$ 2,809,487.12
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (S	16,432	$ 208,326.38
OPIOID COMBINATIONS	15,157	$ 430,875.86
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (N	13,116	$ 324,738.63
CENTRAL MUSCLE RELAXANTS	12,981	$ 224,436.46
HMG COA REDUCTASE INHIBITORS	11,271	$ 377,934.26
DIBENZAPINES	10,180	$ 374,197.46
OPIOID AGONISTS	9,816	$ 383,792.91
ANTIANXIETY AGENTS - MISC.	9,659	$ 149,050.54

2020 Q3

Drug Class Name	Count of Claims	Amt Paid
ANTICONVULSANTS - MISC.	27,353	$ 2,718,570.90
SYMPATHOMIMETICS	18,207	$ 2,750,439.93
SELECTIVE SEROTONIN REUPTAKE INHIBITORS	16,436	$ 212,330.66
OPIOID COMBINATIONS	15,361	$ 435,260.56
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	13,495	$ 283,852.08
CENTRAL MUSCLE RELAXANTS	13,072	$ 221,955.87
HMG COA REDUCTASE INHIBITORS	11,132	$ 383,681.83
DIBENZAPINES	10,195	$ 396,108.69
OPIOID AGONISTS	10,013	$ 492,885.40
ANTIANXIETY AGENTS - MISC.	9,419	$ 144,113.65

Top 10 Classes by Amount Paid

2020 Q4

Drug Class Name	Count of Claims	Amt Paid
ANTIHEMOPHILIC PRODUCTS	126	$ 14,139,357.89
ANTIRETROVIRALS	1,875	$ 4,196,903.68
INSULIN	4,811	$ 3,325,443.06
SYMPATHOMIMETICS	18,738	$ 2,809,487.12
ANTIPSYCHOTICS - MISC.	3,079	$ 2,744,616.60
ANTICONVULSANTS - MISC.	27,055	$ 2,722,609.26
BENZISOXAZOLES	5,992	$ 2,614,160.78
ANTINEOPLASTIC ENZYME INHIBITORS	195	$ 2,231,903.20
CYSTIC FIBROSIS AGENTS	228	$ 2,136,069.30
ANTI-TNF-ALPHA - MONOCLONAL ANTIBODIES	304	$ 1,993,065.59

2020 Q3

Drug Class Name	Count of Claims	Amt Paid
ANTIHEMOPHILIC PRODUCTS	114	$ 13,239,554.37
ANTIRETROVIRALS	1,841	$ 4,032,838.15
INSULIN	4,799	$ 3,247,199.91
SYMPATHOMIMETICS	18,207	$ 2,750,439.93
ANTICONVULSANTS - MISC.	27,353	$ 2,718,570.90
BENZISOXAZOLES	5,967	$ 2,690,060.59
ANTIPSYCHOTICS - MISC.	2,995	$ 2,675,174.38
ANTINEOPLASTIC ENZYME INHIBITORS	203	$ 2,447,970.60
LOCAL ANESTHETICS - TOPICAL	1,903	$ 2,282,470.89
CYSTIC FIBROSIS AGENTS	232	$ 2,175,569.35

cDUR Quarterly Report

Client(s): 'NVM'
Carrier ID: NVM
Account(s): All
Group(s): All
Primary Start Date: October 1, 2020
Primary End Date: December 31, 2020

Claims Summary:

Claim Status	Total Rxs	Total Interventions	% Total Rxs with Interventions
Paid	620,894	141,352	22.8%
Rejected	489,952	173,038	35.3%
Reversed	109,610	34,990	31.9%
Total	***1,220,456***	***349,380***	***28.6%***

cDUR Savings Outcomes Analysis Summary:

Current		Accruing		Total		Total Year to Date	
Successes	Savings	Successes	Savings	Successes	Savings	Successes	Savings
48,265	**$6,091,058**	**24,211**	**$21,733,425**	**72,476**	**$27,824,483**	**208,282**	**$92,521,350**

cDUR Detailed Activity Summary:

Intervention Type	Total	Paid Rxs		Rejected Rxs		Reversed Rxs	
	Interventions	Interventions	% Total Interventions	Interventions	% Total Interventions	Interventions	% Total Interventions
Dosing/Duration (DOSECHEK)	44,102	34,398	78.0%	1,080	2.4%	8,624	19.6%
Drug-Drug Interaction (DDI-DTMS)	117,445	53,464	45.5%	55,783	47.5%	8,198	7.0%
Duplicate Therapy (DUPTHER)	98,787	43,307	43.8%	46,860	47.4%	8,620	8.7%
Drug Safety Screening (CDSAFETY)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Multiple Drug Screening (OVERLAP)	21	8	38.1%	N/A	N/A	13	61.9%
Duplicate Rx (DUPRX)	88,493	10,171	11.5%	68,795	77.7%	9,527	10.8%
Drug Inferred Health State (DINFERRD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Sex Caution (DRUG_SEX)	5	2	40.0%	N/A	N/A	3	60.0%
Drug/Diagnosis Caution (DIAGCAUT)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Age Caution (DRUG_AGE)	7	2	28.6%	N/A	N/A	5	71.4%
Refill Too Soon	520	N/A	N/A	520	100.0%	N/A	N/A
Morphine Equivalent Dose Limit Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Therapeutic Dose Limits Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Allergy Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acute/Maintenance Dose Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total All cDURs	***349,380***	***141,352***	***40.5%***	***173,038***	***49.5%***	***34,990***	***10.0%***

cDUR Detailed Saving Outcomes Summary:

Intervention Type	Current		Accruing		Total		Total Year to Date	
	Successes	Savings	Successes	Savings	Successes	Savings	Successes	Savings
Dosing/Duration (DOSECHEK)	1,415	$1,457,938	1,884	$16,535,590	3,299	$17,993,528	7,539	$42,599,658
Drug-Drug Interaction (DDI-DTMS)	3,763	$523,597	3,852	$883,512	7,615	$1,407,109	21,828	$5,447,459
Duplicate Therapy (DUPTHER)	4,893	$948,348	9,534	$3,061,680	14,427	$4,010,028	28,923	$17,398,460
Drug Safety Screening (CDSAFETY)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Multiple Drug Screening (OVERLAP)	0	$0	0	$0	0	$0	3	$14
Duplicate Rx (DUPRX)	37,746	$3,128,818	8,838	$1,242,984	46,584	$4,371,802	147,512	$26,815,223
Drug Inferred Health State (DINFERRD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Sex Caution (DRUG_SEX)	0	$0	46	$1,404	46	$1,404	45	$3,206
Drug/Diagnosis Caution (DIAGCAUT)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Age Caution (DRUG_AGE)	3	$266	0	$0	3	$266	19	$3,579
Refill Too Soon	445	$32,091	57	$8,254	502	$40,346	2,413	$253,751
Morphine Equivalent Dose Limit Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Therapeutic Dose Limits Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Allergy Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acute/Maintenance Dose Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total All cDURs	***48,265***	***$6,091,058***	***24,211***	***$21,733,425***	***72,476***	***$27,824,483***	***208,282***	***$92,521,350***

Claims Summary:

Column Name	Description
Claim Status	The claims status associated with the RxCLAIM transaction: Paid, Reversed, Rejected •Paid Claims with CDUR edit(s) are those which had an override by a pharmacist •Rejected claims with CDUR edit(s) include both hard and soft rejects •Reversed claims with CDUR edit(s) include Paid claims which were reversed, originating with a message and an override by a pharmacist
Total Rxs	The total number of pharmacy claims with or without a cDUR edit
Total Interventions	The total number of pharmacy claims with at least one cDUR edit
% Total Rxs w/ Interventions	Percentage of all pharmacy claims which had a cDUR edit

cDUR Savings Outcomes Summary:

Column Name	Description
Current	Savings from CDUR interventions which occurred in the current period
Accruing	Savings from CDUR interventions which succeeded prior to the current reporting period, where savings continue to accrue in the current reporting period
Total	Total CDUR savings recognized in the current period (Current + Accruing)
Year To Date	Total CDUR savings recognized since the start of the current year
Successes	cDUR Interventions which resulted in Pharmacy Savings in the Current Period

Edit Type	Short Description	Long Description
ACTMAINT	Acute/Maintenance Dose Screening	Member is taking a medication at a higher dose than recommended based on acute daily use versus maintenance daily use.
ALLERCHK	Drug-Allergy Interaction Screening	Member is taking a medication to which he/she may be allergic.
DDI-DTMS	Drug-Drug Interaction Screening	Member is taking 2 interacting medications and/or medication classes.
DIAGCAUT	Drug-Disease screening using actual member disease profile	Member has a certain diagnosis (as determined by member disease profile) and is taking a medication that worsens the diagnosis.
DINFERRD	Drug-Disease screening using medication history as proxy for determining existing disease states	Member has a certain diagnosis (as determined by drug proxy) and is taking a medication that may worsen the member diagnosis.
DOSECHEK	Identifies if incoming claim exceeds recommended daily dose and/or recommended duration	Member is taking a medication for longer and/or at a higher dose than recommended.
DRUG_AGE	Drug-Age contraindication screening	Member is taking a medication that is not recommended for people of certain ages (pediatric and geriatric).
DRUG_SEX	Drug-sex contraindication screening	Member is taking a medication that is not recommended for his/her gender.
DUPRX	Exact GPI duplication screening	Member is taking 2 medications with the same ingredient.
DUPTHER	Drug class duplication screening	Member is taking 2 medications in the same drug class.
MEDLIMIT	Morphine Equivalent Dose Limit Screening	Member is taking opioids where the total cumulative daily dose exceeds the suggested morphine equivalent dose (MED).
REFILL	Refill Too Soon	Member tried refilling with medicagtion still left of hand from prior fill
THERDOSE	Therapeutic Dose Limits Screening	Member is taking medications where the total cumulative daily dose exceeds the FDA approved maximum dose for the medication.

Nevada Medicaid

RetroDUR

Fee for Service

Third and Fourth Quarter 2020

Q3 2020

Initiative	Sent	Responses	Prescribers	Recipients	Response Rate
Support Act - Opioids and Antipsychotics	98	7	75	98	7.14%
Support Act - Opioids and Benzodiazepine	111	15	81	111	13.51%
CGM	119	30	43	119	25.21%

Q4 2020

Initiative	Sent	Responses	Prescribers	Recipients	Response Rate
CGM II	114	31	49	114	27.19%
Albuterol Initiative Part 1	156	18	124	156	11.54%
Albuterol Initiative Part 2	157	17	120	157	10.83%